FORM PTO-1390 (REV 11-98) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

10031764.093002

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

U.S. APPLICATION NO. (If known, see 37 CFR 1.5): 10/031764

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP00/06769	July 15, 2000	July 27, 1999

TITLE OF INVENTION: NOVEL CYCLOHEXAPEPTIDE COMPOUNDS, PROCESSES FOR THEIR PRODUCTION AND THEIR USE AS A PHARMACEUTICAL

APPLICANT(S) FOR DO/EO/US: BANSI et al

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information.

1. [X] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. [X] This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. [ ] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2)) in English
   a. [X] is transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] has been transmitted by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [ ] A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. [ ] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] have been transmitted by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [ ] have not been made and will not be made.
8. [ ] A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. [X] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)). Unexecuted
10. [ ] A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. [X] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [ ] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [X] A FIRST preliminary amendment.
    [ ] A SECOND or SUBSEQUENT preliminary amendment.
14. [ ] A substitute specification.
15. [ ] A change of power of attorney and/or address letter.
16. [X] Other items or information: International Preliminary Examination Report

U S APPLICATION NO (If known, see 37 CFR 1.5) 10/031764 | INTERNATIONAL APPLICATION NO PCT/EP00/06769 | JC13 Rec'd PCT/PTO 18 JAN 2002 | Docket No. 146.1380

21. [X] The following fees are submitted:

	CALCULATIONS PTO USE ONLY
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)):	
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO **$1000.00**	$1040.00
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$860.00**	
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO **$710.00**	
International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$690.00**	
International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) **$100.00**	
ENTER APPROPRIATE BASIC FEE AMOUNT =	$1040.00
Surcharge of **$130.00** for furnishing the oath or declaration later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total claims	- 20 =		x **$18.00**	$
Independent claims	- 3 =		x **$80.00**	$
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ **$270.00**	$
TOTAL OF ABOVE CALCULATIONS =				$ 1040.00
[ ] Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.			+	$
SUBTOTAL =				$ 1040.00
Processing fee of **$130.00** for furnishing the English translation later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(f)).				$
TOTAL NATIONAL FEE =				$ 1040.00
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$
TOTAL FEES ENCLOSED =				$ 1040.00
			Amount to be refunded:	$
			charged:	$

a. [X] ~~A check in the amount of $~~ PTO Form 2038 for $1040.00 is enclosed. ~~to cover the above fees is enclosed.~~

b. [ ] Please charge my Deposit Account No. _____ in the amount of $ _____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. [X] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 02-2275. A duplicate copy of this sheet is enclosed.

d. [X] Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137 (a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:
Bierman, Muserlian and Lucas
600 Third Avenue
New York, NY 10016

SIGNATURE

Charles A. Muserlian
NAME

19,683
REGISTRATION NUMBER

Our Ref.: 146.1380

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
BANSI et al
PCT/EP00/06769
Serial No.:
Filed: Concurrently Herewith
For: NOVEL...A PHARMACEUTICAL

PCT Date: July 15, 2000

600 Third Avenue
New York, NY 10016
January 16, 2002

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Please amend this application as follows:

IN THE SPECIFICATION:

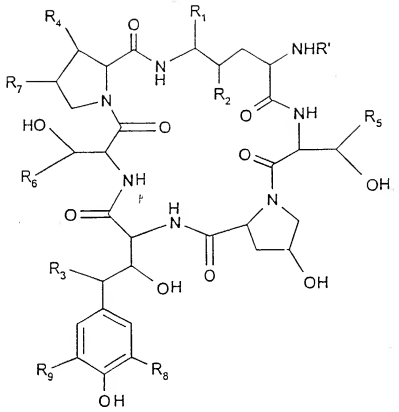
Page 1, before line 1, insert

--This application is a 371 of PCT/EP00/06769 filed July 15, 2000.--

IN THE CLAIMS:

Claim 1 (amended) A compound selected from the group consisting of a cyclohexapeptide compound of the formula

[redacted]



I

wherein,

R^1 is selected from the group consisting of C_1-C_{20} alkyl; C_9-C_{20} alkenyl; C_9-C_{20} alkoxypheny, phenyl, biphenyl, terphenyl, and naphthyl; C_1-C_{12} alkylphenyl, C_8-C_{12} alkenylphenyl, C_1-C_{12} alkoxyphenyl; linoleoyl; palmitoyl; 12-methylmyristoyl; 10,12-dimethylmyristoyl; and $COC_6H_4(p)OC_8H_{17}$,

R_1 and R_3 are independently selected from the group consisting of -OH; -CN; $-CH_2NH_2$; $-N_3$; aryl; substituted aryl; heterocyclyl and substituted heterocyclic with 1-3 of heteroatoms; aminoalkylamino; mono or di-substituted linear or cyclic aminoalkylamino; -OR, wherein, R is C_1-C_{12} alkyl; substituted alkyl of $(CH_2)_n$-X, where n is 1-5 and X is selected from the group consisting of Cl, Br, I, COOY, CN, NH_2 and heterocyclic, Y is selected from the group consisting of C_1-C_6 alkyl; C_2-C_{12}-alkenyl; aryl; fused aryl; substituted aryl;

a heterocyclic containing 1-3 heteroatoms; mono or di-substituted aminoalkyl; and a hydroxy protecting group; and R_3 may additionally be imidazolyl;

R_2 and R_4 are independently -H or -OH;

R_5 is -H or $-CH_3$;

R_6 is selected from the group consisting of -H, $-CH_3$ and $-CH_2CONH_2$;

R_7 is selected from the group consisting of -H, $-CH_3$ and -OH;

R_8 and R_9 are independently -H or $-CH_2$-Sec.amine in which the sec.amine is attached to $-CH_2$ through its N linkage;
and its non-toxic pharmaceutically acceptable salts.

Claim 2 (amended) A compound of claim 1 wherein R_1 is -OH or OR, and R_3 is selected from the group consisting of -OH, -OR and imidazolyl wherein R in each case is selected from the group consisting of C_1-C_{12} alkyl, substituted alkyl of $-(CH_2)_n$-X, where n is 1-5, X is selected from the group consisting of Cl, Br, I, COOY, CN, NH_2 and a heterocyclic, and Y is selected from the group consisting of C_1-C_6 alkyl; $-C_2$-C_{12}-alkenyl; aryl; fused aryl; substituted aryl; a heteroaryl containing 1-3 heteroatoms; a heterocyclic containing 1-3 heteroatoms; a heterocyclic containing 1-3 heteroatoms; mono or di-substituted aminoalkyl; and a hydroxy

protecting group.

Claim 3 (amended) A compound of claim 1 wherein R^1 is selected from the group consisting of linoleoyl, palmitoyl, 12-methylmyristoyl, 10, 12-dimethylmyristoyl and $-COC_6H_4(p)OC_8H_{17}$.

Claim 4 (amended) A compound of claim 1 wherein 1) to the nitrogen atom of the secondary amine are attached at least one member of the group consisting of C_1-C_{12} alkyl, C_2-C_{12} alkenyl, aryl, substituted aryl, alkylaryl and substituted alkylaryl, 2) or the nitrogen atom of the secondary amine is part of a heterocyclic group, optionally substituted by at least one member of the group consisting of C_1-C_6 alkyl, C_1-C_6 alkenyl, aryl, amino, nitro, and halogen, or 3) a fused heterocyclic group, whereby the heterocyclic group contains 1-3 heteroatoms.

Claim 5 (amended) A compound of claim 1 wherein the secondary amine is selected from the group consisting of piperidine, pyrrolidine, 4-methylpiperidine, morpholine, dimethylamine, diisopropylamine, 4-piperidino-piperidine, piperazine, 1-methylpiperazine, 1-(2-fluorophenyl)piperazine, 1-(2-chlorophenyl)piperazine, 1-(2-pyrimidyl)piperazine, 1-(4-fluorophenyl)piperazine, N-(α,α,α-trifluoro-m-tolyl)piperazine, 1-phenylpiperazine, 1-benzylpiperazine, 1-(2-pyridyl)piperazine, 1-(4-pyridyl)piperazine, 1-(4-methylphenyl)piperazine, 1-(2,6-

dimethylphenyl)piperazine, 1-(1-phenylethyl)piperazine, dibenzylamine, N-(tertbutyl)benzylamine and N-(isopropyl)-benzylamine.

Claim 6 (amended) A compound of claim 1, wherein R^1 is 12-methylmyristoyl, R_1 and R_3 are independently selected from the group consisting of -OH, -CN, $-CH_2NH_2$, $-N_3$, aryl, substituted aryl, heterocyclyl and substituted heterocyclyl having 1-3 heteroatoms, aminoalkylamino, and mono or di-substituted linear or cyclic aminoalkylamino, R_5 and R_7 are both $-CH_3$, R_6 is -H, and R_8 and R_9 are both -H.

Claim 7 (amended) An antifungal composition comprising a fungicidally effective amount of a compound of claim 1, and a non-toxic pharmaceutically acceptable carrier.

Claim 9 (amended) A process for the production of a compound of claim 1 comprising:

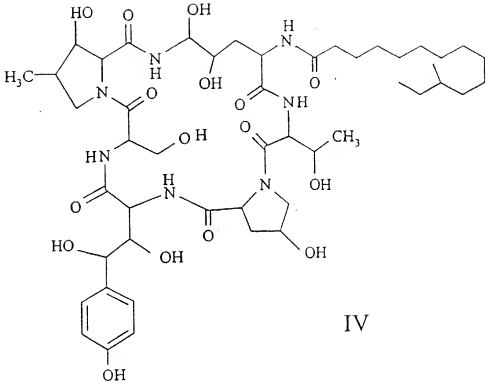
a) reacting a cyclohexapeptide compound of claim 1, wherein R^1, R_2, R_4, R_5, R_6 and R_7 are as defined in claim 1, R_1 and R_3 are both -OH, and R_8 and R_9 are -H, with an alcohol in the presence of an acid in an aprotic solvent at a temperature of 0°C to 60° to obtain the corresponding cyclohexapeptide derivative of claim 1 wherein R^1, R_2, R_4, R_5, R_6 and R_7 are as defined in claim 1, R_1 and R_3 are

independently -Oh or -OR wherein at least one of R_1 or R_3 is -OR, R is selected from the group consisting of C_1-C_{12} alkyl, C_2-C_{12} alkyl, C_2-C_{12} alkenyl, fused aryl, substituted aryl, a heterocyclyl containing 1-3 heteroatoms, mono or di-substituted aminoalkyl, and a hydroxy protecting group, and R_8 and R_9 are -H;

b) reacting the compound of step (a) with a secondary amine in the presence of paraformaldehyde in an aprotic solvent at a temperature of 60°C to 150°C to obtain the desired compound of formula I, isolating and purifying the resulting compound from the reaction mixture in a known manner and optionally converting the compound of formula I into its pharmaceutically acceptable salt in a known manner.

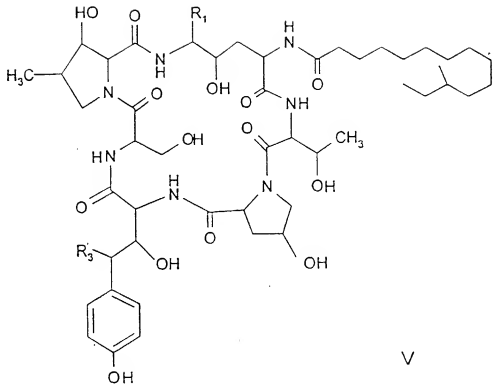
Claim 10 (amended) A process for the preparation of a cyclohexapeptide compound of claim 1 comprising:

a) reacting mulundocandin of the formula



IV

with a nucleophile in the presence of an acid in an aprotic solvent at a temperature of 0°C to 60°C to obtain the corresponding cyclohexapeptide derivative of the formula



V

wherein R_1 and R_3 are -OH or -SR with at least one of R_1 or R_3 is -SR, R is selected from the group consisting of C_1-C_{12} alkyl, substituted alkyl of $-(CH_2)_n-X$, wherein n is 1-5 and X is Cl, Br, I, COOY, CN, NH_2, and a heterocyclic, Y is selected from the group consisting of C_1-C_6 alkyl; C_2-C_{12} alkenyl; aryl; fused aryl; substituted aryl; a heterocyclyl containing 1-3 heteroatoms; mono or di-substituted aminoalkyl; and a hydroxy protecting group;

b) reacting the compound of step (a) with an oxidizing agent in an aqueous medium at a temperature of 20°C to 60°C to obtain the corresponding sulfones of formula V wherein R_1 and R_3 are -OH or $-S(O_2)R$, with at least one of R_1 or R_3 is $-SO_2R$, R is selected from the group consisting of C_1-C_{12} alkyl, substituted alkyl of $-(CH_2)_n-X$, wherein n is 1-5 and X is selected from the group consisting of Cl, Br, I, COOY, CN, NH_2 and a heterocyclic, Y is selected from the group consisting of C_1-C_6 alkyl; C_1-C_{12} alkenyl; aryl; fused aryl; substituted aryl; a heterocyclyl containing 1-3 heteroatoms; mono or di-substituted aminoalkyl; and a hydroxy protecting group;

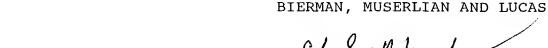
c) reacting the sulfone of step (b) with a nucleophile in a solvent at a temperature of 20°C to 60°C to obtain the desired compound of claim 1, isolating and purifying the resulting compound and optionally converting the compound of claim 1 into its pharmaceutically acceptable salt in a known manner.

REMARKS

The amendment is submitted to insert reference to the PCT

application, to remove multiple dependency from the claims and to conform the claims to the American practice.

Respectfully submitted,
BIERMAN, MUSERLIAN AND LUCAS



Charles A. Muserlian, #19,683
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CAM:sd
Enclosures: Marked-Up Version of Specification and Claims
Return Receipt Postcard

NOVEL CYCLOHEXAPEPTIDE COMPOUNDS, PROCESSES FOR THEIR PRODUCTION AND THEIR USE AS A PHARMACEUTICAL

--This application is a 371 of PCT/EP00/06769 filed July 15, 2000.--

Novel cyclohexapeptide compounds, processes for their production and their use as a pharmaceutical.

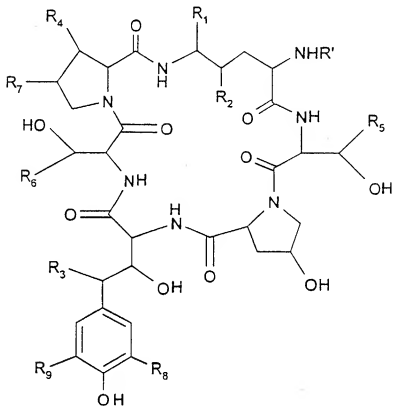
The present invention relates to cyclohexapeptide compounds belonging to the echinocandin class having a substituent group at the ornithine-5, homotyrosine-4 and ortho position of the phenolic hydroxy of the homotyrosine unit, and pharmaceutically acceptable salts thereof. The present invention further relates to processes for the preparation of the novel cyclohexapeptide compounds, to the use of the compounds and their pharmaceutically acceptable salts as pharmaceuticals, in particular to their use in the treatment of fungal infections, and to pharmaceutical compositions comprising the novel compounds or a pharmaceutically acceptable salt thereof.

The search for new and effective antifungal agents has been intensified by the increase in immunological diseases and aggressive immunosuppressive chemotherapy. Present therapeutic options for the treatment of fungal infections are limited to compounds in two classes, the polyenes and the azoles. Due to an increase in the number of isolates, which are resistant to conventional antifungal agents, there presently exists a need for new antifungal and anti-pneumocystis agents. Because there are limited numbers of antifungal agents available for the treatment of life-threatening fungal infections and because resistance may further limit the utility of the newer azoles, there is an urgent need for new antifungal agents with a different mode of action.

Accordingly, the present invention provides novel antifungal cyclohexapeptide compounds represented by general formula I as shown below:

Claims:

1. A cyclohexapeptide compound of the ~~general~~ formula I,



I

wherein,

R^1 is C_1-C_{20} alkyl; C_9-C_{20} alkenyl; C_9-C_{20} alkoxyphenyl; ~~an aryl group selected from~~, phenyl, biphenyl, terphenyl, ~~and~~ naphthyl; C_7-C_{12} alkylphenyl, C_8-C_{12} alkenylphenyl, C_7-C_{12} alkoxyphenyl; linoleoyl; palmitoyl; 12-methylmyristoyl; 10,12-dimethylmyristoyl; ~~or~~ and $-COC_6H_4(p)OC_8H_{17}$,

R_1 and R_3 are independently -OH; -CN; $-CH_2NH_2$; $-N_3$; aryl; substituted aryl; heterocyclyl and substituted heterocyclic with 1-3 of ~~the same or different~~ heteroatoms; aminoalkylamino; mono or di-substituted linear or cyclic aminoalkylamino; -OR, wherein, R is C_1-C_{12} alkyl; substituted alkyl of ~~the type~~ $-(CH_2)_n$-X, where n is 1-5 and X is Cl, Br, I, COOY, CN, NH_2 ~~or~~ and a heterocyclic ~~and where~~ Y is C_1-C_6 ~~linear or branched~~ alkyl; C_2-C_{12}-alkenyl; aryl; fused aryl; substituted aryl; a heterocyclic containing 1-3 heteroatoms; mono or di-

substituted aminoalkyl, and a hydroxy protecting group; and R_3 may additionally be imidazolyl.

R_2 and R_4 are independently -H or –OH;

R_5 is -H or $-CH_3$.

R_6 is -H, $-CH_3$ and $-CH_2CONH_2$.

R_7 is -H, $-CH_3$ and -OH.

R_8 and R_9 are independently -H or $-CH_2$-Sec.amine in which the sec.amine is attached to $-CH_2$ through its N linkage;

and its pharmaceutically acceptable salts.

2. A compound of the formula I as claimed in claim 1 wherein R_1 is –OH or OR, and R_3 is –OH, -OR and imidazolyl wherein R in each case is C_1-C_{12} alkyl, substituted alkyl of the type $-(CH_2)_n$-X, where n is 1-5, X is Cl, Br, I, COOY, CN, NH_2 and a heterocyclic and Y is a C_1-C_6 linear or branched alkyl; C_2-C_{12}-alkenyl; ary; fused aryl; substituted aryl; a heteroaryl containing 1-3 heteroatoms; a heterocyclic containing 1-3 heteroatoms; mono or di-substituted aminoalkyl; and a hydroxy protecting group.

3. A compound of the formula I as claimed in claim 1 or claim 2 wherein R^1 is linoleoyl, palmitoyl, 12-methylmyristoyl, 10, 12-dimethylmyristoyl and $-COC_6H_{4(p)}OC_8H_{17}$.

4. A compound of the formula I as claimed in claim 1, 2 or 3, wherein the nitrogen atom of the secondary amine are attached the same or different groups selected from: C_1-C_{12} alkyl, C_2-C_{12} alkenyl, aryl, substituted aryl, alkylaryl and substituted alkylaryl, or the nitrogen atom of the secondary amine is part of a heterocyclic group, optionally substituted by one or more of C_1-C_6 alkyl, C_1-C_6 alkenyl, aryl, amino, nitro and halogen, or a fused heterocyclic group, whereby the heterocyclic group contains 1-3 of the same or different heteroatoms.

5. A compound of ~~the formula I as claimed in any one of the preceding claims~~, wherein the secondary amine is selected from piperidine, pyrrolidine, 4-methylpiperidine, morpholine, dimethylamine, diisopropylamie, 4-piperidino-piperidine, piperazine, 1-methylpiperazine, 1-(2-fluorophenyl)piperazine, 1-(2-chlorophenyl)piperazine, 1-(2-pyrimidyl)piperazine, 1-(4-fluorophenyl)piperazine, N-(α,α,α-trifluoro-m-tolyl)piperazine, 1-phenylpiperazine, 1-benzylpiperazine, 1-(2-pyridyl)piperazine, 1-(4-pyridyl)piperazine, 1-(4-methylphenyl) piperazine, 1-(2,6-dimethylphenyl)piperazine, 1-(1-phenylethyl)piperazine, dibenzylamine, N-(tert-butyl)benzylamine and N-(isopropyl)benzylamine.

6. A compound of ~~the formula I as claimed in~~ claim 1, wherein R^1 is 12-methylmyristoyl, R_1 and R_3 are independently -OH, -CN, $-CH_2NH_2$, $-N_3$, aryl, substituted aryl, heterocyclyl and substituted heterocyclyl having 1-3 of ~~the same or different~~ heteroatoms, aminoalkylamino, ~~or~~ mono or di-substituted linear or cyclic aminoalkylamino, R_5 and R_7 are both $-CH_3$, R_6 is –H, and R_8 and R_9 are both –H.

7. ~~A pharmaceutical~~ composition comprising ~~an~~ effective amount of ~~the~~ compound of ~~the formula I or a pharmaceutically acceptable salt thereof as claimed in any one of the preceding claims~~, and a pharmaceutically acceptable carrier.

8. A compound ~~of the formula I as claimed in any one of~~ claims 1 ~~to 6~~ or a pharmaceutically acceptable salt thereof for use as an anti-fungal agent.

9. A process for the production of a compound of ~~the general formula I as claimed in claims 1-5~~, comprising ~~the steps of:~~

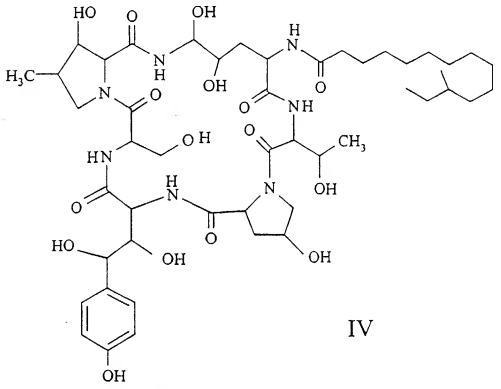
a) reacting a cyclohexapeptide compound of ~~the formula I~~, wherein R^1, R_2, R_4, R_5, R_6 and R_7 are as defined in claim 1, ~~2 or 3~~, R_1 and R_3 are both –OH, and R_8 and R_9 are -H , with an alcohol in the presence of an acid in an aprotic solvent at a temperature ~~ranging from~~ 0°C to 60° to obtain the corresponding cyclohexapeptide derivative of ~~the formula~~ I wherein R^1, R_2,

R_4, R_5, R_6 and R_7 are as defined in claim 1, ~~2 or 3~~, R_1 and R_3 are independently –OH or –OR ~~such that~~ wherein at least one of R_1 or R_3 is -OR, ~~wherein~~ R is ~~a~~ C_1-C_{12} alkyl, C_2-C_{12} alkenyl, fused aryl, substituted aryl, a heterocyclyl containing 1-3 heteroatoms, mono or di-substituted aminoalkyl, ~~or~~ and a hydroxy protecting group, and R_8 and R_9 are -H;

b) reacting the compound ~~s obtained in~~ of step (a) with a secondary amine in ~~the~~ presence of paraformaldehyde in an aprotic solvent at a temperature ~~ranging from~~ of 60°C to 150°C to ~~yield~~ obtain the desired compound of formula I, isolating and purifying the resulting compound ~~of formula I~~ from the reaction mixture in a known manner and ~~if desired~~ optionally converting the compound of formula I into its pharmaceutically acceptable salt in a known manner.

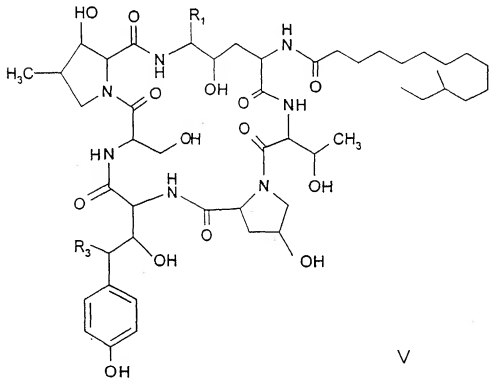
10. A process for the preparation of a cyclohexapeptide compound of ~~the formula I as claimed in any one of claims 1 to 6~~ claim 1, comprising ~~the steps of~~:

a) reacting mulundocandin of the ~~following~~ formula ~~IV~~,



IV

with a nucleophile in presence of an acid in an aprotic solvent at a temperature ranging from 0°C to 60° to obtain the corresponding cyclohexapeptide derivative of formula V



V

wherein R_1 and R_3 are –OH or –SR such that at least one of R_1 or R_3 is -SR wherein R in each case is C_1-C_{12} alkyl, substituted alkyl of the type $-(CH_2)_n$-X, wherein n is 1-5 and X is Cl, Br, I, COOY, CN, NH_2, or a heterocyclic, Y is C_1-C_6 linear or branched alkyl chain; C_2-C_{12} alkenyl; aryl; fused aryl; substituted aryl; a heterocyclyl containing 1-3 heteroatoms; mono or di-substituted aminoalkyl; or a hydroxy protecting group ;

b) reacting the compounds of formula V as obtained in step (a) with an oxidising agent in an aqueous medium at a temperature ranging from 20°C to 60°C to obtain the corresponding sulfones (VI), wherein R_1 and R_3 are –OH or -S

$(O_2)R$, ~~such that~~ at least one of R_1 or R_3 is $-SO_2R$, ~~wherein~~ R is a C_1-C_{12} alkyl, substituted alkyl of ~~the type~~ $-(CH_2)_n$-X, wherein n is 1-5 and X is Cl, Br, I, COOY, CN, NH_2, a heterocyclic, Y is a C_1-C_6 ~~linear or branched~~ alkyl ~~chain~~; C_1-C_{12} alkenyl; aryl; fused aryl; substituted aryl; a heterocyclyl containing 1-3 heteroatoms; mono or di-substituted aminoalkyl, ~~or~~ a hydroxy protecting group;

c) reacting the sulfone ~~(VI) obtained in~~ step (b) with a nucleophile in a solvent at a temperature ~~ranging from~~ 20°C to 60°C to obtain the desired compound of ~~the formula I~~, isolating and purifying the resulting compound ~~of the formula I from the reaction mixture in a known manner~~ and ~~if desired~~, converting the compound of ~~formula I~~ into its pharmaceutically acceptable salt in a known manner.

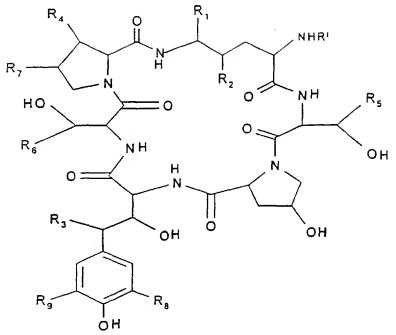
NOVEL CYCLOHEXAPEPTIDE COMPOUNDS, PROCESSES FOR THEIR PRODUCTION AND THEIR USE AS A PHARMACEUTICAL

Novel cyclohexapeptide compounds, processes for their production and their use as a pharmaceutical.

The present invention relates to cyclohexapeptide compounds belonging to the echinocandin class having a substituent group at the ornithine-5, homotyrosine-4 and ortho position of the phenolic hydroxy of the homotyrosine unit, and pharmaceutically acceptable salts thereof. The present invention further relates to processes for the preparation of the novel cyclohexapeptide compounds, to the use of the compounds and their pharmaceutically acceptable salts as pharmaceuticals, in particular to their use in the treatment of fungal infections, and to pharmaceutical compositions comprising the novel compounds or a pharmaceutically acceptable salt thereof.

The search for new and effective antifungal agents has been intensified by the increase in immunological diseases and aggressive immunosuppressive chemotherapy. Present therapeutic options for the treatment of fungal infections are limited to compounds in two classes, the polyenes and the azoles. Due to an increase in the number of isolates, which are resistant to conventional antifungal agents, there presently exists a need for new antifungal and anti-pneumocystis agents. Because there are limited numbers of antifungal agents available for the treatment of life-threatening fungal infections and because resistance may further limit the utility of the newer azoles, there is an urgent need for new antifungal agents with a different mode of action.

Accordingly, the present invention provides novel antifungal cyclohexapeptide compounds represented by general formula I as shown below:



I

wherein

R^1 is C_9-C_{20} alkyl; C_9-C_{20} alkenyl; C_9-C_{20} alkoxyphenyl; an aryl group selected from: phenyl, biphenyl, terphenyl and naphthyl; C_1-C_{12} alkylphenyl, C_2-C_{12} alkenylphenyl, C_1-C_{12} alkoxyphenyl; linoleoyl; palmitoyl; 12-methylmyristoyl; 10,12-dimethylmyristoyl; or $-COC_6H_4(p)OC_8H_{17}$;

R_1 and R_3 are independently -H; -OH; -CN; $-CH_2NH_2$; $-N_3$; aryl; substituted aryl; heterocyclyl and substituted heterocyclyl with 1-3 of the same or different heteroatoms; aminoalkylamino; mono or di-substituted linear or cyclic aminoalkylamino; -OR, wherein, R is C_1-C_{12} alkyl; substituted alkyl of the type $-(CH_2)_n$-X ,where n is 1-5 and X is Cl, Br, I, COOY, CN, NH_2 or a heterocyclic and where Y = C_1-C_6 linear or branched alkyl; C_2-C_{12}-alkenyl; aryl; fused aryl; substituted aryl; a heterocyclic containing 1-3 heteroatoms; mono or di-substituted aminoalkyl; or a hydroxy protecting group; or R_3 is imidazolyl;

R_2 and R_4 are independently -H or –OH;

R_5 is -H or $-CH_3$;

R_6 is -H, $-CH_3$ or $-CH_2CONH_2$;

R_7 is -H, $-CH_3$ or –OH;

R_8 and R_9 are independently -H or -CH_2-Secondary amine, the secondary amine being attached to –CH_2 through its N-linkage; and its pharmaceutically acceptable salts.

To the nitrogen atom of the secondary amine are attached the same or different groups selected from: C_1-C_{12} alkyl, C_2-C_{12} alkenyl, aryl, substituted aryl, alkylaryl and substituted alkylaryl, or the nitrogen atom of the secondary amine is part of a heterocyclic group, optionally substituted by one or more of: C_1-C_6 alkyl, C_2-C_6 alkenyl, aryl, amino, nitro and halogen, or a fused heterocyclic group, whereby the heterocyclic group in each case contains 1-3 of the same or different heteroatoms.

Examples of suitable secondary amines are piperidine, pyrrolidine, 4-methyl-piperidine, morpholine, dimethylamine, diisopropylamie, 4-piperidino-piperidine, piperazine, 1-methylpiperazine, 1-(2-fluorophenyl)piperazine, 1-(2-chlorophenyl)piperazine, 1-(2-pyrimidyl)piperazine, 1-(4-fluorophenyl)piperazine, N-(α,α,α-trifluoro-m-tolyl)piperazine, 1-phenylpiperazine, 1-benzylpiperazine, 1-(2-pyridyl)piperazine, 1-(4-pyridyl)piperazine, 1-(4-methylphenyl) piperazine, 1-(2,6-dimethylphenyl)piperazine, 1-(1-phenylethyl)piperazine, dibenzylamine, N-(tert-butyl)benzylamine, and N-(isopropyl)benzylamine.

In a preferred first embodiment, R_1 is -OH or -OR and R_3 is -OH, -OR or imidazolyl, wherein R in each case is C_1-C_{12} alkyl, substituted alkyl of the type -$(CH_2)_n$-X, where n is 1-5, X is Cl, Br, I, COOY, CN, NH_2 or a heterocyclic and Y is a C_1-C_6 linear or branched alkyl; C_2-C_{12}-alkenyl; aryl; fused aryl; substituted aryl; a heterocyclic containing 1-3 heteroatoms; mono or di-substituted aminoalkyl; or a hydroxy protecting group.

Ideally in the first embodiment R_8 and /or R_9 is –CH_2-secondary amine.

In an alternative preferred embodiment R^1 is 12-methylmyristoyl, R_1 and R_3 are independently -OH, -CN, -CH_2NH_2, -N_3, aryl, substituted aryl, a heterocyclyl or a substituted heterocyclyl, having the heterocyclyl in each case 1-3 of the same or different heteroatoms, aminoalkylamino, or mono or di-substituted linear or cyclic

aminoalkylamino, R_2 and R_4 are both –OH, R_5 and R_7 are both $–CH_3$, R_6 is –H, and R_8 and R_9 are both –H.

The compounds provided by this invention are semi-synthetic cyclic hexapeptides derived from cyclic peptides, which are produced by culturing various microorganisms. A number of cyclic peptides are known in the literature, including mulundocandin, sporiofungin, echinocandin B and aculeacin.

These cyclic hexapeptides have closely related structures with some modification of the cyclic peptide and / or the N-acyl fatty acid chain. For example mulundocandin has a methyl-myristoyl side chain, aculeacin A has a palmitoyl side chain, echinocandin B has a linoleoyl side chain and pneumocandin Ao has a di-methylmyristoyl side chain. The naturally occurring cyclic hexapeptides of the echinocandin class have a labile C-O bond and C-N bond at the ornithine-5 position as disclosed in US-A-5,378,804 issued January 3, 1995.

According to the present invention there are further provided processes for the preparation of novel cyclohexapeptide compounds of general formula I above.

The invention is described herein using the terms defined below unless otherwise specified.

Throughout the specification and appended claims, a given chemical formula or name shall encompass all optical and stereoisomers as well as racemic mixtures where such isomers and mixtures exist.

As used herein, the term "C_1-C_{12} alkyl" refers to a straight or branched alkyl chain having from one to twelve carbon atoms. Typical C_1-C_{12} alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, t-butyl, pentyl, hexyl, octyl, nonyl, decyl, undecyl, dodecyl and the like. The term "C_1-C_{12} alkyl" includes within its definition the term "C_1-C_6 alkyl".

The term "C_9-C_{20} alkyl" refers to a straight or branched alkyl chain having from nine to twenty carbon atoms.

The term "C_1-C_{12} alkenyl" refers to a straight or branched chain hydrocarbon having from one to twelve carbon atoms, with at least one unsaturation. Typical alkenyl groups are groups such as vinyl, 1-propen-2-yl, 1-buten-4-yl, 2-buten-4-yl and 1-penten-5-yl.

The term "C_9-C_{20} alkenyl" refers to a straight or branched alkyl chain having from nine to twenty carbon atoms with at least one saturation.

The term "C_9-C_{20} alkoxy" refers to a straight or branched alkyl chain having from nine to twenty carbon atoms attached to an oxygen atom. Typical C_9-C_{20} alkoxy groups are, for example, decyloxy, and dodecyloxy.

The term "substituted alkyl" refers to alkyl groups which may be substituted with up to three substituent groups at any available point of attachment.

The term "cycloalkyl" refers to a species of alkyl containing from 3 to 15 carbon atoms without altering or resonating double bonds between carbon atoms.

The term "aryl" refers to, for example, a phenyl which is optionally substituted by one or more substituents such as halogen, alkyl, alkoxy or nitro.

The term "fused aryl" refers to a bicyclic or polycyclic ring system such as benzene ring having any two adjacent carbon atoms in common. Typical examples of fused aryl groups are naphthalene and anthracene.

The term "heteroatom" refers to N, O, S, and P.

The term "heterocyclic" refers to a 3, 5, 6 or 7 membered ring having 1 to 3 hetero atoms which may be nitrogen, oxygen or sulphur, including pyrrolyl, pyrrolidinyl, pyridonyl, pyridyl, pyrimidyl, pyrazolyl, imidazolyl, isoxazolyl, furyl, thienyl, oxazolyl, thiazolyl, piperidyl, morphinyl, oxazolidinyl, thiazolidinyl, pyrazolidinyl, imidazolidinyl and piperazinyl.

The term "hydroxyprotecting group" refers to a substituent of an hydroxy group that is commonly employed to block or protect the hydroxy functionality while reactions are carried out on the other functional groups on the compound. Examples of such hydroxy protecting groups include tetrahydropyranyl, methoxymethyl, methylthiomethyl, t-butyl, t-amyl, trityl, benzyl, allyl, trimethylsillyl and (t-butyl)dimethylsilyl. The species of hydroxy protecting group is not critical so long as the derivatized hydroxy group is stable to the conditions of the subsequent reaction(s) and can be removed at the appropriate point without disrupting the remainder of the molecule. Preferred hydroxy protecting groups are benzyl and methyl. The term "protected hydroxy" refers to a hydroxy group bonded to one of the above hydroxy protecting groups.

Further examples of hydroxy protecting groups are described in T. W. Greene, "Protective Groups in Organic Synthesis" John Wiley and Sons, New York, N. Y. (2nd edition, 1991) Chapters 2 and 3.

One process for the preparation of cyclohexapeptide compounds of the general formula I above according to the present invention comprises:

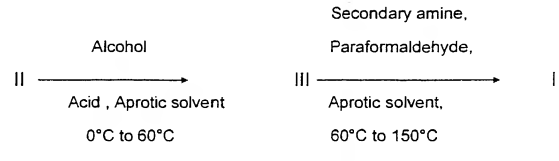
a) reacting a cyclohexapeptide compound of the general formula I above, wherein R^1, R_2, R_4, R_5, R_6 and R_7 are as defined above in the general formula I, R_1 and R_3 are both –OH, and R_8 and R_9 are -H (compound II), with an alcohol in the presence of an acid in an aprotic solvent at a temperature ranging from 0°C to 60° to obtain the corresponding cyclohexapeptide derivative of the formula I wherein R^1, R_2, R_4, R_5, R_6 and R_7 are as defined in the general formula I, R_1 and R_3 are –OH or –OR, such that at least one of R_1 or R_3 is –OR, wherein R is C_1-C_{12} alkyl, C_2-C_{12} alkenyl, fused aryl, substituted aryl, a heterocyclyl containing 1-3 heteroatoms, mono or di-substituted aminoalkyl, or a hydroxy protecting group, and R_8 and R_9 are –H (compound III);

b) reacting the compound III obtained in step (a) with an appropriate secondary amine in the presence of paraformaldehyde in an aprotic solvent at a temperature ranging from 60°C to 150°C to yield the desired compound of

formula I, isolating and purifying the resulting compound of formula I from the reaction mixture in a known manner and if desired, converting the compound of formula I into its pharmaceutically acceptable salt in a known manner.

The final compounds of formula I can be purified by procedure well known in the art such as crystallization followed by filtration. Alternatively the solvent can be removed by extraction, evaporation and the intermediates can be purified if required by chromatography with solid support such as silica gel, alumina, RP-8 or RP-18.

The described process for the preparation of the cyclohexapeptide compound of general formula I is illustrated as follows:



SCHEME 1

The reaction of step (b) wherein the intermediate compounds III are reacted with a secondary amine in the presence of paraformaldehyde is known in the art as a Mannich Reaction.

The starting compounds II may be natural products such as mulundocandin, echinocandin B, aculeacin, pneumocandin Ao , pneumocandin Bo, pneumocandin Co and cilofungin.

In the process of the present invention, the alcohol used in step (a) may be an alkyl alcohol such as methanol or an aryl alcohol such as benzyl alcohol.

For step (a), suitable acids include strong organic acid such as trifluoroacetic acid, p-toluene sulphonic acid, camphor sulphonic acid or a lewis acid such as borontrifluoride etherate, titanium tetrachloride.

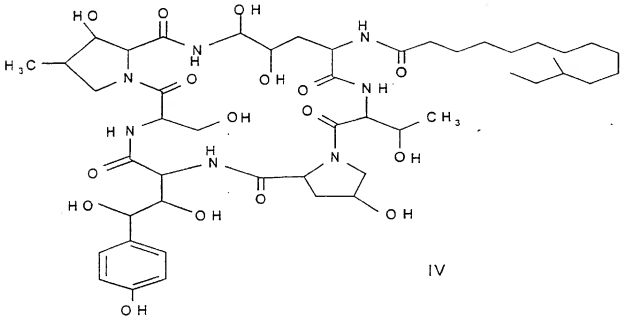
Suitable aprotic solvents used in steps (a) and (b) are selected from 1,4-dioxane, N,N-dimethylformamide(DMF), dimethylsulfoxide(DMSO), tetrahydrofuran(THF), toluene. The preferred one is 1,4-dioxane.

In step (b), the said secondary amines include compounds in which the nitrogen contains the same or different C_1-C_{12} alkyl, C_2-C_{12} alkenyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl groups, and compounds in which the nitrogen atom of the secondary amine may be a part of a heterocyclic or substituted heterocyclic or fused heterocyclic. The heterocyclics may contain 1-3 of the same or different heteroatoms. Substituted heterocyclics may contain substituent(s) such as C_1-C_6 alkyl, C_1-C_6 alkenyl, aryl, amino, nitro and/or halogens.

Some representative examples of secondary amines are listed below: piperidine, pyrrolidine, 4-methylpiperidine, morpholine, dimethylamine, diisopropylamie, 4-piperidino-piperidine, piperazine, 1-methylpiperazine, 1-(2-fluorophenyl)piperazine, 1-(2-chlorophenyl)piperazine, 1-(2-pyrimidyl)piperazine, 1-(4-fluorophenyl)piperazine, N-(α,α,α-trifluoro-m-tolyl)piperazine, 1-phenylpiperazine, 1-benzylpiperazine, 1-(2-pyridyl)piperazine, 1-(4-pyridyl)piperazine, 1-(4-methylphenyl) piperazine, 1-(2,6-dimethylphenyl)piperazine, 1-(1-phenylethyl)piperazine, dibenzylamine, N-(tert-butyl)benzylamine and N-(isopropyl)benzylamine.

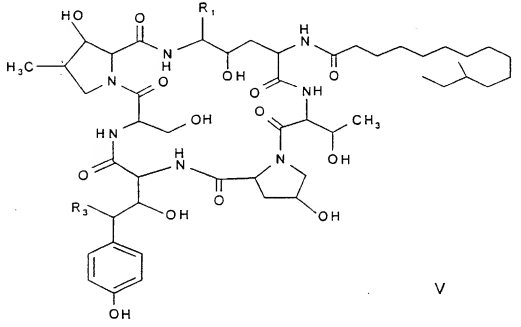
The present invention provides a second process for the preparation of compounds of the general formula I comprising:

a) reacting mulundocandin of the following formula IV,



IV

with a nucleophile such as a thiol or a thioether in presence of an acid in an aprotic solvent at a temperature ranging from 0°C to 60° to obtain the corresponding cyclohexapeptide derivatives of formula V;



V

wherein R_1 and R_3 are independently –OH or –SR such that at least one of R_1 or R_3 is –SR, wherein R is C_1-C_{12} alkyl, substituted alkyl of the type -$(CH_2)_n$-X, wherein n is 1-5 and X is Cl, Br, I, COOY, CN, NH_2, or a heterocyclic and Y is a C_1-C_6 linear or branched alkyl; C_2-C_{12} alkenyl; aryl; fused aryl; substituted aryl; heterocyclyl containing 1-3 heteroatoms; mono or di-substituted aminoalkyl; or a hydroxy protecting group ;

b) reacting the compounds of formula V as obtained in step (a) with an oxidising agent in an aqueous medium at a temperature ranging from 20°C to 60°C to obtain the corresponding sulfones of the formula VI, wherein in formula V above R_1 and R_3 are independently –OH or -S (O_2)R, such that at least one of R_1 or R_3 is $-SO_2R$, wherein R is a C_1-C_{12} alkyl, substituted alkyl of the type -$(CH_2)_n$-X, wherein n is 1-5 and X is Cl, Br, I, COOY, CN, NH_2, a heterocyclic, Y is a C_1-C_6 linear or branched alkyl chain; C_2-C_{12} alkenyl; aryl; fused aryl; substituted aryl; heteroaryl containing 1-3 heteroatoms; heterocyclyl containing 1-3 heteroatoms; mono or di-substituted aminoalkyl; or a hydroxy protecting group;

c) reacting the sulfone (VI) obtained in step (b) with an appropriate nucleophile such as a carbon or nitrogen nucleophile in an appropriate solvent at a temperature ranging from 20°C to 60°C to obtain the desired compound of the formula I, isolating and purifying the resulting compound of the formula I from the reaction mixture in a known matter and, if desired, converting the compound of formula I into its pharmaceutically acceptable salt in a known manner

The final compound of formula I can be purified by procedure well known in the art such as crystallisation followed by filtration. Alternatively the solvent can be removed by extraction, evaporation and the intermediate can be purified if required by chromatography with solid support such as silica gel, alumina, RP-8 or RP-18.

The process for the preparation of the cyclohexapeptide compounds of general formula I is illustrated as follows:

thiother or thiol,	oxidising agent,	Nucleophile,
IV ⟶	V ⟶	VI ⟶ I
acid, aprotic solvent	aqueous medium	aprotic solvent
0°C to 60°C	20°C to 60°C	20°C to 60°C

SCHEME 2

The starting, compound, Mulundocandin, is a naturally occurring cyclic lipopeptide, which is isolated from the cultured broth of a strain of Aspergillus sydowi, a microorganism (Indian Patent No. 162032; The Journal of Antibiotics, Vol. XL No. 3, 275-277). Mulundocandin is useful as an antibiotic.

In the process of the present invention the said nucleophile used in step (a) may be a thioether such as methylthioglycolate or an aryl thiol such as thiophenol.

Step (a) is carried out in presence of an acid which may be a strong organic acid such as trifluoroacetic acid, p-toluene sulphonic acid, camphor sulphonic acid or a lewis acid such as boron trifluoride etherate, titanium tetrachloride.

Suitable aprotic solvents used in steps (a) and (c) are selected from 1,4-dioxane, N, N-dimethylformamide(DMF), dimethylsulfoxide(DMSO), tetrahydrofuran(THF) and toluene. The preferred one is 1, 4-dioxane.

In step (b), the suitable oxidising agent includes OXONE® ($KHSO_5.KHSO_4.K_2SO4$:: 2:1:1; obtained from Aldrich Chemicals), hydrogen peroxide and metachloroperbenzoic acid. The preferrred one is OXONE®.

The said aqueous medium used in the oxidation step is usually a mixture of solvents consisting of water and a water soluble organic solvent such as acetonitrile, dimethylformamide, dimethylsulfoxide and tetrahydrofuran. About 1:1 v/v mixture of the solvents is preferred. The preferred water soluble organic solvent is acetonitrile.

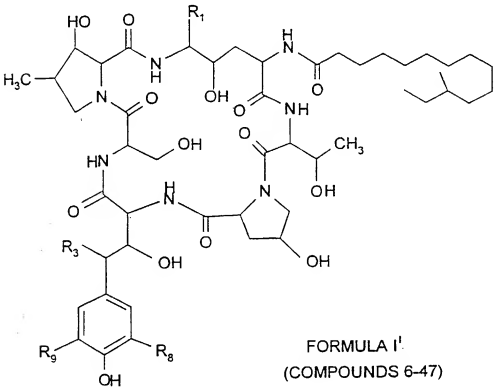
In step (c), the said nucleophile includes a carbon nucleophile or a nitrogen nucleophile.

The carbon nucleophile may be a cyanide such as sodium cyanide, potassium cyanide and lithium cyanide.

The nitrogen nucleophile may be selected from an amine, azide, heterocyclyl, substituted heterocyclyl (containing 1-3 of the same or different heteroatoms), and aminoalkylamino compounds.

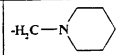
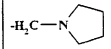
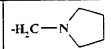
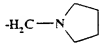
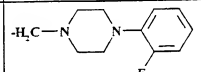
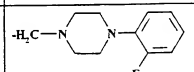
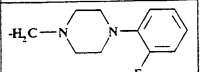
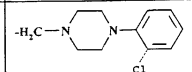
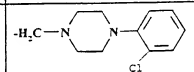
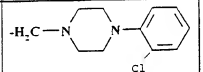
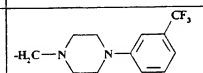
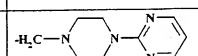
In the second process of the present invention the nucleophilic substitution may take place either at ornithine-5 position only or at both the ornithine-5 and homotyrosine-4 positions depending on the intermediates formed in step (a).

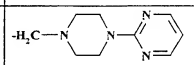
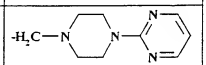
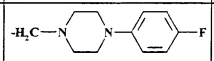
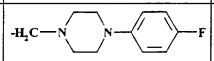
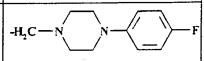
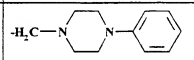
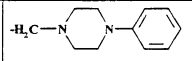
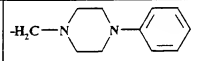
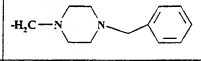
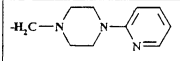
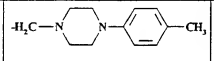
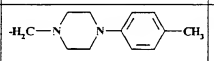
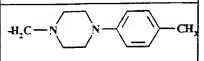
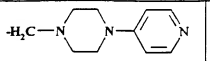
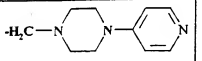
The preferred representatives of cyclohexapeptide compounds of formula I' below are listed in the following Table I.

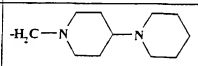
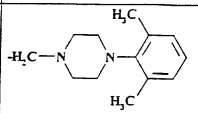
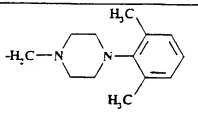
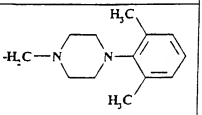
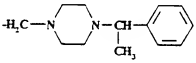
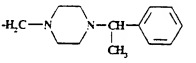
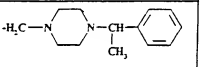
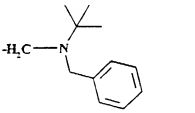
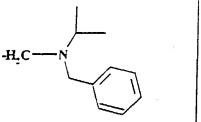


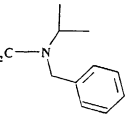
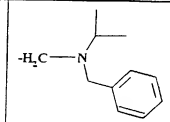
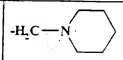
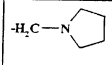
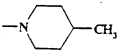
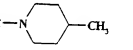
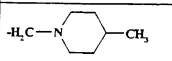
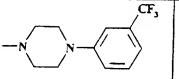
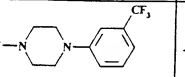
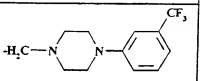
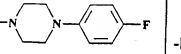
FORMULA I'
(COMPOUNDS 6-47)

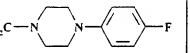
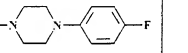
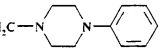
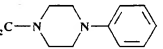
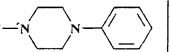
TABLE I

COMPD NO	R_1	R_3	R_8	R_9
6	$-OCH_2Ph$	-OH		-H
7	$-OCH_2Ph$	-OH		-H
8	$-OCH_2Ph$	-OH		
9	$-OCH_2Ph$	-OH		-H
10	$-OCH_2Ph$	-OH		
11	$-OCH_2Ph$	-OH		-H
12	$-OCH_2Ph$	-OH		
13	$-OCH_2Ph$	-OH		-H
14	$-OCH_2Ph$	-OH		-H

COMPD NO	R_1	R_3	R_8	R_9
15	-OCH_2Ph	-OH		
16	-OCH_2Ph	-OH		-H
17	-OCH_2Ph	-OH		
18	-OCH_2Ph	-OH		-H
19	-OCH_2Ph	-OH		
20	-OCH_2Ph	-OH	-$CH_2N(CH_2Ph)_2$	-H
21	-OCH_2Ph	-OH		-H
22	-OCH_2Ph	-OH		-H
23	-OCH_2Ph	-OH		-H
24	-OCH_2Ph	-OH		
25	-OCH_2Ph	-OH		

COMPD NO	R_1	R_3	R_8	R_9
26	-OCH_2Ph	-OH		-H
27	-OCH_2Ph	-OH		-H
28	-OCH_2Ph	-OH		
29	-OCH_2Ph	-OH		-H
30	-OCH_2Ph	-OH		
31	-OCH_2Ph	-OH		-H
32	-OCH_2Ph	-OH		-H

COMPD NO	R_1	R_3	R_8	R_9
33	$-OCH_2Ph$	-OH		
34	$-OCH_2Ph$	$-OCH_2Ph$		-H
35	$-OCH_2Ph$	$-OCH_2Ph$		
36	$-OCH_2Ph$	$-OCH_2Ph$		-H
37	$-OCH_2Ph$	$-OCH_2Ph$		
38	$-OCH_2Ph$	$-OCH_2Ph$		-H
39	$-OCH_2Ph$	$-OCH_2Ph$		
40	$-OCH_2Ph$	$-OCH_2Ph$		-H
41	$-OCH_2Ph$	$-OCH_2Ph$		
42	$-OCH_2Ph$	$-OCH_2Ph$	$-CH_2N(CH_2Ph)_2$	-H
43	$-OCH_3$	-OH		-H

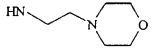
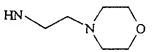
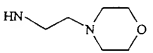
COMPD NO	R_1	R_3	R_8	R_9
44	$-OCH_3$	-OH		
45	$-OCH_3$	-OH		-H
46	$-OCH_3$	-OH		
47	$-OCH_2OH$			H

The compounds (6-47) listed in the Table 1 are prepared from Mulundocandin (Formula IV above, compound 1) as the starting material whereby in the general formula I R^1 is 12-methylmyristoyl; R_1, R_2, R_3 and R_4 each represent -OH, R_5 and R_7 each represents $-CH_3$, R_6 represents –H and R_8 and R_9 are -H.

The preferred representatives of intermediate compounds III are compounds 2-5 as described in the experimental section of the specification.

The further preferred representative compounds given in Table II have the general formula I^1 above in which R^8 and R^9 are H and R_1 and R_3 are the groups shown in the Table.

TABLE II

COMPD NO	R_1	R_3
54	CN	-OH
55	CH_2NH_2	-OH
56		-OH
57		-OH
58	CN	CN
59	N_3	N_3
60		

The preferred representatives of intermediate compounds of general formula V and VI are compounds 49-53 as described in the experimental section of the specification.

The compound 55 as shown in Table II is obtained by reduction of compound 54 with a reducing agent such as $CoCl_2$-$NaBH_4$ or by hydrogenation using raney nickel as a catalyst in presence of ammonia in alcoholic solvent.

The compounds of general formula I, if desired may be converted into their pharmaceutically acceptable salts.

Preferred pharmaceutically acceptable acid addition salts are those formed with mineral acid such as hydrochloric acid and those formed with organic acid such as acetic acid.

The compounds of present invention are soluble in lower alcohols and polar aprotic solvents such as N,N-dimethylformamide (DMF), dimethyl sulfoxide (DMSO) and pyridine.

The compounds of present invention are useful for the control of both filamentous fungi and yeast. They are especially adaptable to be employed for the treatment of mycotic infections in mammals, especially those caused by Candida species such as C.albicans, C.tropicals and C.neoforma and Aspergillus species such as A.fumigatus, A.flavus and A.niger. These type of infections are usually found in immunocompromised patients such as those suffering from AIDS.

The compounds of formula I of the present invention and pharmaceutically acceptable salts thereof may be administered orally, intramuscularly, intravenously or by other modes of administration. Pharmaceutical compositions which contain the compound according to the invention or a pharmaceutically acceptable salt or derivative thereof singly or in combinations can be prepared according to standard techniques by mixing the compound(s) with one or more pharmacologically acceptable excipients and/or auxiliaries such as fillers, emulsifiers, lubricants, masking flavours colorants or buffer substances, and converting the mixture into a suitable pharmaceutical form such as tablets, coated tablets, capsules or a suspension or solution suitable for enteral or parental administration. Further details of the production of suitable pharmaceuticals may be obtained from the literature which relates to the echinocandin type of antibiotics.

As cusomary, the galenic formulation and the method of administration as well as the dosage range which are suitable in a specific case depend on the species to be treated and on the state of the respective condition or disease, and can be optimized using methods known in the art. On an average, the daily dose of a compound of the formula I in a patient of about 75 kg weight is at least 0.001 mg to at most 10 mg, preferably at most 1.0 mg.

The compounds disclosed herein have basic amino-functionality at the ornithine/homotyrosine unit(s), imparting solubility of compounds through their salts.

The following examples illustrate the invention but are not to be considered as limiting the scope of the invention.

The terms infrared spectra, electron spray ionization mass spectra, proton nuclear magnetic resonance spectra, ^{13}C-nuclear magnetic resonance spectra, melting point, ultraviolet spectra, thin layer chromatography, high pressure liquid chromatography are abbreviated "IR", "ESI MS", "^1H NMR", "^{13}C NMR", "m.p.", "UV", "TLC", "HPLC" respectively.

In conjunction with the ^1H NMR spectra, the following abbreviations are used : "s" is singlet, "d" is doublet, "t" is triplet, "q" is quartet, "dd" is doublet of doublet, "br" is broad, "br.s" is broad singlet, "br.d" is broad doublet, "br.t" is broad triplet, "br.m" is broad multiplet, "J" indicates the coupling constant in Hertz (hz). ^1H NMR, ^{13}C NMR, IR, MS, HPLC, m.p. data refers to the free base of the subject compound, unless otherwise mentioned.

Melting points were recorded on a Kofler hot-plate apparatus and are uncorrected. IR spectra were obtained on a Perkin-Elmer 157 spectrophotometer using KBr pellets. ^1H NMR were recorded on a Brucker ACP-300 MHz instrument using CD_3OD as solvent, unless otherwise mentioned. The chemical shifts are expressed in delta (δ) values (parts per million downfield from tetramethylsilane). ^{13}C NMR were recorded on a Brucker ACP-300 and the chemical shifts are expressed in ppm. Electron spray ionization mass spectra (ESI MS) were recorded on a VG QUATTRO II instrument. Perkin Elmer 235 HPLC were used for purification (Semipreparative column- Knauer Eurosphere 100, C-18 column, 250 x 16 mm, 10 μm, λ = 220 & 270 nm) and for checking purity (Analytical column -YMC-Pack, AQ-313 S-5 120A ODS, C-18 column, 6 x 250 mm, 5 μm, λ = 220 & 270 nm) of the compounds, according to the invention.

Procedure for the preparation of compounds 2 & 3 :-

To a stirred solution of mulundocandin 1 (5.2 g, 5.15 mmol) in anhydrous 1,4-dioxane (150 ml), under nitrogen atmosphere was added anhydrous benzyl alcohol

(10.45 g, 96.6 mmol), and a catalytic amount of p-toluenesulfonic acid (0.32 g, 1.66 mmol) and the resulting reaction mixture was stirred at ambient temperature for 1 hr. Reaction progress was monitored by TLC (20 % MeOH/$CHCl_3$). TLC analysis after 1 hr. showed no starting compound. The reaction was quenched at 5-10 °C by the addition of saturated aqueous $NaHCO_3$ and evaporated to smaller volume (25 ml). The above mixture was diluted with water (250 ml), extracted with n-butanol(3 x 150 ml) and washed with water (200 ml) followed by brine (200 ml). Combined organic extract was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to give crude gummy product, which was then dissolved in a minimum amount of methanol(15 ml), adsorbed on silica gel (1:1 w/w), and was subjected to silica gel flash column chromatography. 0-15 % MeOH/$CHCl_3$ was used as 5 % step gradient elution. Evaporation of the appropriate fractions gave white compound 2 (3.8 g, 67.13 %) and 3 (0.82 g, 13.37 %).

Compound 2 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-benzyloxy-23-((1S)-2-benzyloxy-1-hydroxy-2-(4-hydroxyphenyl)ethyl)-2,11,15-trihydroxy-6-((1R)-1-hydroxy-ethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxo-perhydrodiazolo[2,1-c:2,1-/][1,4,7, 10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^1H NMR : 7.28 – 7.41 (m, 5H, OCH_2Ph), 7.17 (d, 2H, 8.37 Hz., Ar-H), 6.78 (d, 2H, 8.37 hz., Ar-H), 4.68 (s, 2H, OCH_2Ph)

^{13}C NMR spectrum of ornithine5-benzylmulundocandin (in DMSO-d_6) :

172.07, 171.51, 170.46, 170.27, 169.59, 168.14, 156.57, 138.78, 132.47, 128.19, 127.94, 127.35, 127.08, 114.65, 79.01, 75.19, 74.24, 73.19, 69.23, 68.99, 68.66, 68.04, 66.10, 62.27, 60.82, 56.29, 55.67, 53.49, 51.84, 51.28, 49.23, 37.26, 36.99, 35.99, 35.13, 34.72, 33.73, 29.36, 29.03, 28.90, 28.52, 26.45, 25.42, 19.38, 19.06, 11.19, 10.81.

IR(KBr): 3350-3450 br, 2930, 1650 br, 1615, 1520, 1450, 1385(sharp), 1220, 1070 cm^{-1}.

ESI MS(ES+): for $C_{55}H_{83}N_7O_{16}$

Calculated : 1098.292

Found : $(M+Na)^+$ = 1120.7 (base peak), 567.4.

UV(MeOH): λ_{max} : 206, 225, 277 nm (ε = 31040, 14016, 1595)

Compound 3 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-benzyloxy-23-((1S)-2-benzyloxy-1-hydroxy-2-(4-hydroxyphenyl)ethyl)-2,11,15-trihydroxy-6-((1R)-1-hydroxy-ethyl)-20-hydroxy-methyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c:2,1-*f*][1,4,7,10,13,16]hexa-azacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^{1}H NMR : 7.24 – 7.31 (m, 5H, 2 x OCH_2Ph), 7.12 (d, 2H, 8.55 Hz., Ar-H), 6.74 (d, 2H, 8.55 hz., Ar-H), 4.4 – 4.53 (2 x s, 4H, 2 x OCH_2Ph)

IR(KBr):-3350-3450 br, 2930, 1650 br, 1615, 1520, 1450, 1385(sharp), 1220, 1070 cm^{-1}.

ESI MS(ES+): for $C_{62}H_{89}N_7O_{16}$

Calculated : 1188.416

Found : $(M+Na)^+$ = 1210.3(base peak), 1146.2, 567.4.

UV(MeOH) : λ_{max} : 209, 228, 275 nm (ε = 30025, 14113, 1767)

Procedure for the preparation of compounds 4 & 5 :-

To a stirred solution of mulundocandin 1 (2.2 g, 2.18 mmol) in anhydrous 1,4-dioxane (50 ml), under nitrogen atmosphere was added anhydrous methanol(6.0 ml, 147.9 mmol), and a catalytic amount of p-toluenesulfonic acid (0.12 g, 0.624 mmol) and the resulting reaction mixture was stirred at ambient temperature for 0.5 hr. Reaction progress was monitored by TLC (20 % MeOH/$CHCl_3$). The reaction workup and purification process are similar to that described for compounds 2 and 3. Evaporation of the appropriate fractions gave white compound 4 (1.55 g, 69.53 %) and 5 (0.109g, 4.82 %).

Compound 4 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-23-((1S,2S)-1,2-dihydroxy-2-(4-hydroxy phenyl)ethyl)-2,11,15-trihydroxy-6-((1R)-1-hydroxyethyl)-20-hydroxy-methyl-12-methoxy-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo-[2,1-c:2,1-/][1,4,7,10,13,16]hexaazacyclo- henicosin -9-yl]-12-methyltetradecan-amide.

Partial ^{1}H NMR : 7.19 (d, 2H, 8.55 hz), 6.89 (d, 2H, 8.55 hz), 5.12 (d, 1H, 1.65 hz), 3.38 (s, 3H, OCH_3).

IR(KBr):-3300-3400 br, 2920, 1660 br, 1625, 1515, 1440, 1385, 1230, 1070 cm^{-1}

ESI MS(ES+): for $C_{49}H_{79}N_7O_{16}$

Calculated : 1022.194

Found : $(M+Na)^+$ = 1044.5 (base peak)

1030.4, 1013.4, 1000.5, 892.5, 567.3

UV(MeOH): λ_{max} : 206, 223, 277 nm (ε = 12258, 8085, 557)

Compound 5 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-23-((1S)-1-hydroxy-2-(4-hydroxyphenyl)-2-methoxyethyl)-2,11,15-trihydroxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-12-methoxy-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo-[2,1-c:2,1-/][1,4,7,10,13,16]hexaazacyclohe-nicosin-9-yl]-12-methyltetradecan-amide.

Partial ^{1}H NMR : 7.25, 7.15 (2 x d, 2H, 8.37 hz), 6.82 (2 x d(merged), 2H, 8.37 hz), 5.12 (br, 1H), 3.42 (2 x s, 6H, 2 x OCH_3) .

IR(KBr): 3300-3400 br, 2915, 1650 br, 1630, 1520, 1445, 1390(sharp),1240, 1080 cm^{-1}

ESI MS(ES+): for $C_{50}H_{81}N_7O_{16}$

Calculated :1036.221

Found : $(M+Na)^+$ = 1058.6 (base peak)

1014.5, 840.5, 567.2.

UV(MeOH): λ_{max}: 205, 223, 275 nm (ε = 11514, 5526, 506)

Compound 6 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-23-((1S,2S)-2-(3-(1-azinanyl-methyl)-4-hydroxyphenyl)-1,2-dihydroxyethyl)-12-benzyloxy-2,11,15-trihydroxy-6-((1R)-1-hydroxy- ethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c:2,1-*f*] [1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

In a 25 ml oven dried round-bottom flask were placed ornithine-5-benzylmulundocandin 2 (0.1 g, 0.091 mmol), piperidine (0.077 g, 0.91 mmol), paraformaldehyde (0.0546 g, 1.82 mmol), and anhydrous 1,4-dioxane (10 ml) and the ingredients were heated under reflux for 2 hr. Reaction progress was monitored by TLC (20 % MeOH/$CHCl_3$). TLC analysis after 2 hr. showed no starting compound. Reaction mixture was cooled to ambient temperature, the solvent was evaporated under vacuum to leave a crude residue, which was then diluted with water (100 ml) and extracted with *n*-butanol (3 x 50 ml). The n-butanol extract was washed with water (100 ml) followed by brine (100 ml). Combined organic extract was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to give impure product, which was then dissolved in minimum amount of methanol (5 ml), adsorbed on silica gel (1:1 w/w), and was subjected to silica gel flash column chromatography. 0-25 % MeOH/$CHCl_3$ was used as 5 % step gradient elution. Evaporation of the appropriate fractions gave white compound 6 (0.03 g, 27.57 %).

Partial ^1H NMR : 7.28-7.41 (m, 5H,-OCH_2Ph), 7.17 (dd, 1H, 8.32 hz & 1.8 hz), 7.0 (d, 1H, 1.8 hz), 6.78 (d, 1H, 8.37 hz), 5.31 (d, 1H, 1.65 hz), 4.68 (s, 2H,-OCH_2Ph), 4.05 (s, 2H, d), 2.7 (m, 4H), 1.45-1.7 (m, 6H).

IR(KBr): 3300-3400 br, 2920, 1660 br, 1630, 1540, 1460, 1260, 1075 cm^{-1}

ESI MS(ES+): for $C_{61}H_{94}N_8O_{16}$

Calculated : 1195.451

Found :$(M+Na)^+$ = 1217.5

1132.5 (base peak), 1088.4, 808.3, 567.2.

UV(MeOH): λ_{max}: 210, 232, 276 nm (ε = 60230, 33362, 4381)

General procedure for the preparation of compounds 7-46:-

To a stirred solution of compound 2, 3 or 4 (1 eq.) in anhydrous 1,4-dioxane (10-40 ml) was slowly added secondary amine (10 eq.) and paraformaldehyde (20 eq.) and the ingredients were heated under reflux(100-120°C) for 2-31 hr. Reaction progress was monitored by TLC (20 % MeOH/$CHCl_3$). The reaction workup and purification process are similar to the described for compound 6. Stoichiometric ratios of starting compound, secondary amine, paraformaldehyde and anhydrous 1,4-dioxane are given in Table-III. Yield, m.p., reaction time, molecular formula and molecular weight of the compounds (7-46) are given in Table-III.

Compound 7 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-23-((1S,2S)-2-(3-(1-azolanylmethyl)-4-hydroxyphenyl)-1,2-dihydroxyethyl)-12-benzyloxy-2,11,15-trihydroxy-6-((1R)-1-hydroxy- ethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c:2,1-*f*] [1,4,7,10,13,16] hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^1H NMR : 7.3-7.4 (m, 5H, OCH_2Ph), 7.25 (dd, 1H, 8.55 hz & 1.9 hz), 7.15 (d, 1H, 1.9 hz), 6.85 (d, 1H, 8.55 hz), 5.33 (d, 1H, 1.65 hz), 4.65 (s, 2H,-OCH_2Ph), 4.12 (s, 2H), 3.3 (m, 4H), 2.05 (m, 4H).

IR(KBr): 3300-3400 br, 2930, 1650, 1625, 1530, 1450, 1260, 1080 cm^{-1}

ESI MS(ES+): for $C_{60}H_{92}N_8O_{16}$

Calculated : 1181.424

Found : $(M+Na)^+$ = 1204.7

1132.5 (base peak),1056.5,567.2.

UV(MeOH): λ_{max}: 207, 231, 280 nm (ε = 49807, 15214, 3515)

Compound 8 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-benzyloxy-23-((1S,2S)-2-(3,5-di(1-azo- lanylmethyl)-4-hydroxyphenyl)-1,2-dihydroxyethyl)-2,11,15-trihydroxy-6-((1-R)-1-hydroxy-ethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c:2,1-*f*] [1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^{1}H NMR : 7.28-7.41 (m, 5H, OCH_2Ph), 7.09 (s, 2H), 5.33 (br, 1H), 4.68 (s, 2H, OCH_2Ph), 4.13 (s, 4H), 3.1 (m, 8H), 1.95 (m, 8H).

IR(KBr): 3300-3400 br, 2930, 1650, 1625, 1530, 1450, 1260, 1080 cm^{-1}

ESI MS(ES+): for $C_{65}H_{101}N_9O_{16}$

Calculated : 1264.557

Found : $(M+Na)^+$ = 1287.6

1215.5, 1144.5 (base peak),567.1.

Compound 9 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-benzyloxy-23-((1S,2S)-2-(3-(4-(2-fluorophenyl)-1,4-diazinan-1-ylmethyl)-4-hydroxyphenyl)-1,2-dihydroxyethyl)-2,11,15-tri- hydroxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxo- perhydrodiazolo[2,1-c:2,1-/][1,4,7,10,13,16] hexaazacyclohenicosin-9-yl]-12-methyltetra- decanamide.

Partial ^{1}H NMR : 7.28-7.41 (m, 5H, OCH_2Ph), 7.17 (dd, 1H, 8.11 hz & 1.86 hz), 7.0-7.15 (m, 5H), 6.8 (d, 1H, 8.11 hz), 5.32 (d, 1H, 1.8 hz), 4.67 (s, 2H, OCH_2Ph), 3.85 (s, 2H), 3.18 (m, 4H), 2.82 (m, 4H) .

IR(KBr): 3300-3400 br, 2910, 1640 br, 1615, 1515, 1490(sharp), 1440, 1225, 1060 cm^{-1}

ESI MS(ES+): for $C_{65}H_{96}FN_9O_{16}$

Calculated : 1290.527

Found : $(M+Na)^+$ = 1312.6

1290.7, 1132.6 (base peak),1088.4, 567.0.

UV(MeOH): λ_{max}: 207, 231, 276 nm (ε = 41469, 14667, 4107)

Compound 10 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-benzyloxy-23-((1S,2S)-2-(3,5-di(4-(2-fluorophenyl)-1,4-diazinan-1-ylmethyl)-4-hydroxyphenyl)-1,2-dihydroxyethyl)-2,11,15-trihy- droxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhy- drodiazolo[2,1-c:2,1-/][1,4,7,10,13,16] hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^{1}H NMR : 7.28-7.41 (m, 5H, OCH_2Ph), 7.16 (s, 2H), 7.0-7.15 (m, 8H), 5.32 (d, 1H, 1.8 hz), 4.67 (s, 2H, OCH_2Ph), 3.9 (s, 4H), 3.2 (br, 8H), 2.9 (br, 8H).

IR(KBr): 3300-3400 br, 2910, 1660 br, 1620, 1520, 1490, 1440, 1235, 1060 cm^{-1}

ESI MS(ES+): for $C_{77}H_{109}F_2N_{11}O_{16}$

Calculated : 1482.763

Found : $(M+Na)^+$ = 1504.9

1483.0, 1324.7, 1194.7, 1146.6, 567.3.

UV(MeOH): λ_{max} : 207, 235, 278 nm (ε = 40426, 11675, 2626)

Compound 11 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-benzyloxy-23-((1S,2S)-2-(3-(4-(2-chlorophenyl)-1,4-diazinan-1-ylmethyl)-4-hydroxyphenyl)-1,2-dihydroxyethyl)-2,11,15-tri- hydroxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoper- hydrodiazolo[2,1-c:2,1-*f*][1,4,7,10,13,16] hexaazacyclohenicosin-9-yl]-12-methyltetradecana- mide.

Partial ^{1}H NMR : 7.28-7.40, 7.15-7.21, 7.05-7.12 (3 x m, 11H, Ar-H), 6.81 (d, 1H, 8.01 hz, Ar-H), 5.31 (d, 1H, 1.86 hz), 4.67 (s, 2H, OCH_2Ph), 3.88 (s, 2H), 3.18 (br, 4H), 2.9 (br, 4H).

IR(KBr): 3350-3450 br, 2935, 1650 br, 1630, 1530, 1450, 1260, 1130, 1080 cm^{-1}

ESI MS(ES+): for $C_{66}H_{96}ClN_9O_{16}$

Calculated : 1306.982

Found : $(M+Na)^+$ = 1329.6

1308.5, 1198.8, 132.7 (base peak).

UV(MeOH): λ_{max} : 209, 249, 276 nm (ε = 44379, 8061, 3572)

Compound 12 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-benzyloxy-23-((1S,2S)-2-(3,5-di(4-(2-chlorophenyl)-1,4-diazinan-1-ylmethyl)-4-hydroxyphenyl)-1,2-dihydroxy-ethyl)-2,11,15-trihy-droxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhy- drodiazolo[2,1-c:2,1-*f*][1,4,7,10,13,16] hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^{1}H NMR : 7.28-7.40, 7.15-7.12, 7.06-7.13 (3 x m, 15H, Ar-H), 5.33 (br, 1H), 4.67 (s, 2H, OCH_2Ph), 3.87 (s, 4H), 3.18 (br, 8H), 2.95 (br, 8H) .

IR(KBr): 3350-3450 br, 2930, 1645 br, 1630, 1530, 1450, 1260, 1130, 1075 cm^{-1}

ESI MS(ES+): for $C_{77}H_{109}Cl_2N_{11}O_{16}$

Calculated : 1515.672

Found : $(M+Na)^+$ = 1538.7

1144.3 (base peak),567.4.

Compound 13 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-benzyloxy-23-((1S,2S)-1,2-dihydroxy-2-(4-hydroxy-3-(4-(3-trifluromethylphenyl)-1,4-diazinan-1-ylmethyl)phenyl)ethyl)-2,11,15-trihy- droxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhy- drodiazolo[2,1-c:2,1-/][1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^{1}H NMR :7.28-7.45 (m, 5H, OCH_2Ph), 7.18-7.26(m, 4H), 7.15 (dd, 1H, 8.13 hz & 1.86 hz),7.1 (d, 1H, 1.86 hz), 6.8 (d, 1H, 8.13 hz), 5.32 (d, 1H, 1.86 hz),4.68(s, 2H, OCH_2Ph), 3.8 (s, 2H), 2.85 (br, 8H).

^{13}C NMR Spectrum :

176.82, 174.90, 174.23, 174.09, 173.56, 172.72, 170.74, 159.17, 153.73, 153.65, 140.71, 133.76, 133.35, 133.12, 132.93, 131.67, 130.70, 130.08, 129.66, 129.39, 128.44, 124.11, 123.53, 121.13, 117.53, 113.82, 81.45, 77.57, 76.85, 76.57, 72.22, 71.04, 70.68, 69.04, 64.18, 63.26, 62.07, 60.36, 59.16, 57.88, 56.43, 54.67, 54.28, 53.64, 51.89, 39.84, 39.45, 38.56, 37.64, 36.46, 35.96, 31.89, 31.58, 31.47, 31.36, 31.11, 28.99, 27.85, 20.57, 20.46, 12.56, 12.01.

IR(KBr): 3350-3450 br, 2930, 1660 br, 1635, 1540, 1455, 1330, 1260, 1180, 1130, 1075 cm^{-1}

ESI MS(ES+): for $C_{67}H_{96}F_3N_9O_{16}$

Calculated : 1340.535

Found :$(M+Na)^+$=1362.6

1266.6, 1132.6 (base peak), 1024.6, 808.3, 567.0.

UV(MeOH): λ_{max} : 208, 240, 255 nm (ε = 4902, 904, 1609)

Compound 14 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-benzyloxy-23-((1S,2S)-2-(3-(4-(1,3-diazin-2-yl)-1,4-diazinan-1-ylmethyl)-4-hydroxyphenyl-1,2-dihydroxyethyl)-2,11,15-trihy- droxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoper- hydrodiazolo[2,1-c:2,1-*f*][1,4,7,10,13,16] hexaazacyclohenicosin-9-yl]-12-methyltetradeca-namide.

Partial ^{1}H NMR : 8.36 (d, 2H, 7.8 hz), 7.29-7.41 (m, 5H, OCH_2Ph), 7.19 (dd, 1H, 8.01 hz & 1.86 hz, Ar-H), 7.08 (d, 1H, 1.86 hz, Ar-H), 6.81 (d, 1H, 8.01 hz, Ar-H), 6.65 (t, 1H, 9.3 hz & 4.5 hz, Ar-H), 5.31 (d, 1H, 1.53 hz), 4.68 (s, 2H, OCH_2Ph), 3.85 (s, 2H), 3.95 (br. 4H), 2.75 (br, 4H).

IR(KBr): 3350-3450 br, 2940, 1660 br, 1630, 1590(s), 1550, 1450, 1390, 1365, 1270, 1075 cm^{-1}

ESI MS(ES+): for $C_{64}H_{95}N_{11}O_{16}$

Calculated : 1274.512

Found :$(M+Na)^+$ = 1296.5

1274.8, 1167.7, 1132.7 (base peak), 1088.6, 567.3.

Compound 15 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-benzyloxy-23-((1S,2S)-2-(3,5-di(4-(1,3-diazin-2-yl)-1,4-diazinan-1-ylmethyl)-4-hydroxyphenyl-1,2-dihydroxyeth-yl)-2,11,15-trihydro- xy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodi- azolo [2,1-c:2,1-*f*] [1,4,7,10,13,16] hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^{1}H NMR : 8.35 (d, 4H, 7.8 hz, Ar-H), 7.26-7.41 (m, 5H, OCH_2Ph), 7.13 (s, 2H), 6.63 (t, 2H, 9.6 hz, 4.8 hz, Ar-H), 5.31 (br.s, 1H), 4.68 (s, 2H, OCH_2Ph), 3.9 (s, 4H), 3.95 (br. 8H), 2.75 (br., 8H).

IR(KBr): 3350-3450 br, 2925, 1660 br, 1630, 1590(s), 1550, 1450, 1390, 1360, 1265, 1080 cm^{-1}

ESI MS(ES+): for $C_{73}H_{107}N_{15}O_{16}$

Calculated : 1450.773

Found :$(M+Na)^+$ = 1472.7

1451.7,1308.4, 1144.6(base peak), 567.2.

Compound 16 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-benzyloxy-23-((1S,2S)-1,2-dihydroxy-2-(3-(4-(4-flurophenyl)-1,4-diazinan-1-ylmethyl)-4-hydroxyphenyl)ethyl)-2,11,15-trihydroxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo [2,1-c:2,1-*f*] [1,4,7,10,13,16] hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^{1}H NMR : 7.28-7.41 (m, 5H, OCH_2Ph), 7.18 (dd, 1H, 8.40 hz & 1.53 hz, Ar-H), 7.08 (d, 1H, 1.53 hz, Ar-H), 7.0 (d, 4H, 8.16 hz, Ar-H), 6.8 (d, 1H, 8.40 hz, Ar-H), 5.33 (d, 1H, 1.5 hz), 4.68 (s, 2H, OCH_2Ph), 3.85 (s, 2H), 3.20 (br., 4H), 2.80 (br., 4H).

IR(KBr): 3350-3450 br, 2920, 1645 br, 1615, 1509, 1430, 1225, 1065 cm^{-1}

ESI MS(ES+): for $C_{66}H_{96}FN_9O_{16}$

Calculated : 1290.527

Found :$(M+Na)^+$ = 1312.4

1291.7, 1182.6, 1164.7, 1132.5 (base peak), 1088, 567.1.

Compound 17 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-benzyloxy-23-((1S,2S)-2-(3,5-di(4-(4-flurophenyl)-1,4-diazinan-1-ylmethyl)-4-hydroxyphenyl)-1,2-dihydroxyethyl)-2,11,15–trihydro- xy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodi-azolo [2,1-c:2,1-*f*] [1,4,7,10,13,16] hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^{1}H NMR : 7.28-7.41 (m, 5H, OCH_2Ph), 7.14 (s, 2H, Ar-H),7.0 (d, 8H, 7.41 hz, Ar-H), 5.33 (d, 1H, 1.8 hz), 4.68 (s, 2H, OCH_2Ph), 3.85 (s, 4H), 3.22 (br, 8H), 2.83 (br, 8H).

IR(KBr): 3350-3450 br, 2920, 1645 br, 1615, 1509, 1430, 1225, 1065 cm^{-1}

ESI MS(ES+): for $C_{77}H_{109}F_2N_{11}O_{16}$

Calculated : 1482.763

Found :$(M+Na)^+$ = 1504.8

1482.9, 1225.7, 1268.6, 1195.8, 1144.7, 1088.6, 567.3.

UV(MeOH): λ_{max} : 210, 233, 285 nm (ε = 75574, 36321, 8063)

Compound 18 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-benzyloxy-23-((1S,2S)-1,2-dihydroxy-2-(4-hydroxy-3-(4-phenyl)-1,4-diazinan-1-ylmethyl)phenyl)ethyl)-2,11,15-trihydroxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c: 2,1-*f*] [1,4,7,10,13,16] hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^{1}H NMR : 7.28-7.41(m,5H, OCH_2Ph), 7.21-7.27 (m, 2H, Ar-H), 7.19 (dd, 1H, 8.40 hz & 2.16 hz, Ar-H), 7.08 (d,1H, 2.16 hz), 7.02 (d, 2H, 8.40 hz), 6.90 (t, 1H, 7.20 hz), 6.80 (d, 1H, 8.40 hz), 5.31 (d, 1H, 2.25 hz), 4.68 (s, 2H, OCH_2Ph), 3.85 (s, 2H), 3.27 (br, 4H), 2.80 (br, 4H,).

IR(KBr): 3300-3400 br, 2910, 1645 br, 1610, 1515, 1430, 1215, 1060 cm^{-1}

ESI MS(ES+): for $C_{66}H_{97}N_9O_{16}$

Calculated : 1272.537

Found :$(M+Na)^+$= 1294.7

1272.4, 1132.5 (base peak), 1089.9, 808.5, 567.2.

UV(MeOH): λ_{max} : 207, 230, 246, 279 nm (ε = 47454, 14338, 12697, 3314)

Compound 19 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-benzyloxy-23-((1S,2S)-1,2-dihydroxy- 2-(4-hydroxy-3,5-di(4-phenyl)-1,4-diazinan-1-ylmethyl)phenyl)ethyl)-2,11,15-trihydroxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo- [2,1-c:2,1-*f*][1,4,7,10,13,16] hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^{1}H NMR : 7.25-7.41 (m, 9H, OCH_2Ph), 7.14 (s, 2H, Ar-H), 7.03 (d, 4H, 8.70 hz, Ar-H), 6.88 (tt, 2H, 7.5 hz & 1.2 hz, Ar-H), 5.31 (d, 1H, 1.53 hz), 4.68 (s, 2H, OCH_2Ph), 3.85 (s, 4H), 3.87 (br, 8H,), 2.80 (br, 8H).

IR(KBr): 3300-3400 br, 2910, 1650 br, 1625, 1525, 1440, 1220, 1060 cm^{-1}

ESI MS(ES+): for $C_{77}H_{111}N_{11}O_{16}$

Calculated : 1446.782

Found :$(M+Na)^+$= 1468.8

1446.8, 1306.8, 1176.8, 1144.6 (base peak), 1036.7, 567.2.

UV(MeOH): λ_{max} : 208, 248, 282 nm (ε = 65504, 32883, 4472)

Compound 20 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-benzyloxy-23-((1S,2S)-2-(3-dibenzyl aminomethyl-4-hydroxyphenyl)-1,2-dihydroxyethyl)-2,11,15-trihydroxy-6-((1R)-1-hydroxy- ethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c:2,1-*f*] [1,4,7,10, 13, 16] hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^{1}H NMR : 7.28-7.42 (m, 15H, OCH_2Ph, 2 x NCH_2Ph), 7.17 (dd, 1H, 8.64 hz & 2.16 hz, Ar-H), 7.09 (d, 1H, 2.16 hz, Ar-H), 6.79 (d, 1H, 8.64 hz, Ar-H), 5.31 (d, 1H, 1.53 hz), 4.68 (s, 2H, OCH_2Ph), 3.63-3.7 (2 x s, 6H).

^{13}C NMR Spectrum :

176.83, 174.96, 174.15, 174.08, 173.5, 172.66, 170.62, 158.97, 140.66, 139.11, 134.0, 131.51, 130.44, 130.02, 129.76, 129.67, 129.57, 129.34, 128.86, 124.07, 117.41, 81.46, 77.39, 76.77, 76.48, 72.21, 72.12, 71.05, 70.63, 69.01, 64.09, 63.15, 59.53, 59.24, 57.88, 56.74, 56.36, 53.55, 51.99, 39.80, 39.38, 38.54, 37.60, 36.43, 35.95, 31.87, 31.55, 31.42, 31.36, 31.06, 28.96, 27.83, 20.42, 12.53, 11.98.

IR(KBr): 3300-3400 br, 2910, 1640 br, 1615, 1515, 1430, 1240, 1060 cm^{-1}

ESI MS(ES+): for $C_{70}H_{98}N_8O_{16}$

Calculated : 1307.582

Found :$(M+Na)^+$ = 1330.7

1132.6 (base peak),1024.4, 567.2.

UV(MeOH): λ_{max} : 206, 225, 279 nm (ε = 37234, 8761, 15135)

Compound 21 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-23-((1S,2S)-2-(3-(4-benzyl-1,4-diazinan-1-ylmethyl)-4-hydroxyphenyl)-1,2-dihydroxyethyl)-12-benzyloxy-2,11,15-trihydroxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c: 2,1-*f*][1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^{1}H NMR : 7.28-7.43 (m, 10H, OCH_2Ph, $-NCH_2Ph$),7.18 (dd, 1H, 8.64 hz & 1.86 hz, Ar-H), 7.03 (d, 1H, 1.86 hz, Ar-H), 6.78 (d,1H, 8.64 hz, Ar-H), 5.31 (d, 1H, 2.04 hz), 4.68 (s, 2H, $-OCH_2Ph$), 3.58-3.62 (2 x s, 4H), 3.18, 2.68 (2 x t, 8H).

IR(KBr): 3300-3400 br, 2930, 1650 br, 1625, 1520, 1450, 1390, 1260, 1070 cm^{-1}

ESI MS(ES+): for $C_{67}H_{99}N_9O_{16}$

Calculated : 1286.563

Found :$(M+Na)^+$= 1309.6

1132.5 (base peak), 1088.3, 567.2.

UV(MeOH): λ_{max} : 208, 229, 280 nm (ε = 42242, 12359, 2648)

Compound 22 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-23-((1S,2S)-2-(3-(4-(2-azinyl)-1,4-diaz- inan-1-ylmethyl)-4-hydroxyphenyl-1,2-dihydroxyethyl)-12-benzyloxy-2,11,15-trihydroxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodi- azolo[2,1-c:2,1-/][1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^{1}H NMR : 8.1-8.16 (m, 1H, Ar-H), 7.6 (m, 1H, Ar-H), 7.3-7.45 (m, 5H, -OCH_2Ph), 7.18 (dd, 1H, 8.37 hz & 1.41 hz, Ar-H), 7.08 (d, 1H, 1.41 hz, Ar-H), 6.89 (m, 1H, Ar-H), 6.8 (d, 1H, 8.37 hz, Ar-H), 6.75 (m, 1H, Ar-H), 5.31 (d, 1H, 1.53 hz), 4.68 (s, 2H, -OCH_2Ph), 3.8 (s, 2H), 3.6 (m, 4H), 2.72 (m, 4H).

IR(KBr): 3300-3400 br, 2930, 1640 br, 1620, 1520, 1430, 1375, 1235, 1060 cm^{-1}

ESI MS(ES+): for $C_{65}H_{96}N_{10}O_{16}$

Calculated : 1273.524

Found :$(M+Na)^+$ = 1295.7

1273.7, 1132.5, 808.4, 567.2.

UV(MeOH): λ_{max} : 208, 248, 299 nm (ε = 43844, 27725, 5899)

Compound 23 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-benzyloxy-23-((1S,2S)-1,2-dihydroxy-2-(4-hydroxy-3-(4-(4-methylphenyl)-1,4-diazinan-1-ylmethyl)phenyl)ethyl)-2,11,15-trihydroxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo- [2,1-c:2,1-/] [1,4,7,10,13,16] hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^{1}H NMR : 7.29-7.43 (m, 5H, -OCH_2Ph), 7.18 (dd, 1H, 8.64 hz & 1.53 hz), 7.06-7.12 (m, 3H, Ar-H), 6.93 (d, 2H, 8.64 hz, Ar-H), 6.79 (d, 1H, 8.64 hz, Ar-H),

5.31 (d, 1H, 1.53 hz), 4.68 (s, 2H, -OCH_2Ph), 3.81 (s, 2H), 3.2 (br, 4H), 2.78 (br, 4H), 2.38 (s, 3H, Ar-CH_3).

IR(KBr): 3300-3400 br, 2930, 1640 br, 1620, 1520, 1430, 1375, 1235, 1060 cm^{-1}

ESI MS(ES+): for $C_{67}H_{99}N_9O_{16}$

Calculated : 1286.583

Found :$(M+Na)^+$ = 1309.6

1273.7, 1132.5, 808.4, 567.2.

UV(MeOH): λ_{max} : 209, 230, 247, 279 nm (ε = 71176, 61764, 20808, 5147)

Compound 24 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-benzyloxy-23-((1S,2S)-1,2-dihydroxy-2-(4-hydroxy-3,5-di(4-(4-methylphenyl)-1,4-diazinan-1-ylmethyl)phenyl)ethyl)-2,11,15-trihydro- xy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodi- azolo [2,1-c:2,1-f] [1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^1H NMR : 7.29-7.43 (m, 5H, -OCH_2Ph), 7.14 (s, 2H), 7.1 (d, 4H, 8.64 hz), 6.92 (d, 4H, 8.64 hz), 5.33 (d, 1H, 1.86 hz), 4.68 (s, 2H, -OCH_2Ph), 3.82 (s, 4H), 3.21 (br, 8H), 2.73 (br, 8H), 2.29 (s, 6H, 2 x Ar-CH_3).

IR(KBr): 3350-3450 br, 2940, 1655 br, 1630, 1519(sharp), 1450, 1385(sharp), 1060 cm^{-1}

ESI MS(ES+): for $C_{79}H_{115}N_{11}O_{16}$

Calculated : 1474.835

Found :$(M+Na)^+$ = 1496.8

1474.6, 1389.1, 1320.5, 1144.4 (base peak), 1036.4, 567.4.

UV(MeOH): λ_{max} : 210, 242, 284 nm (ε = 62037, 26909, 5900)

Compound 25 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-benzyloxy-23-((1S,2S)-2-(3,5-di(4-(4-azinyl)-1,4-diazinan-1-ylmethyl)-4-hydroxyphenyl-1,2-dihydroxyethyl)-2,11,15-trihydroxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-

5,8,14,19,22,25-hexaoxoperhydrodiazolo- [2,1-c:2,1-
/][1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.
Partial ^{1}H NMR : 8.15-8.22 (m, 4H, Ar-H), 7.25-7.43 (m, 5H, -OCH_2Ph), 7.14 (s, 2H, Ar-H), 7.0 (m, 4H, Ar-H), 5.31 (br, 1H), 4.68 (s, 2H, -OCH_2Ph), 3.81 (s, 4H), 3.65 (br, 8H) , 2.73 (br, 8H) .
IR(KBr): 3350-3450 br, 2920, 1650 br, 1610, 1540, 1510, 1440, 1385(sharp), 1230, 1070 cm^{-1}
ESI MS(ES+): for $C_{75}H_{109}N_{13}O_{16}$
Calculated : 1448.457
Found :$(M+Na)^+$ = 1470.6
1449.6, 1307.5, 1199.4, 1177.8, 1036.3.
UV(MeOH): λ_{max} : 208, 237, 262 nm (ε = 75379, 10463, 41034)

Compound 26:

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-23-((1S,2S)-2-(3-(4-(1-azinanyl)-1-azina- nylmethyl)-4-hydroxyphenyl)-1,2-dihydroxyethyl)-12-benzyloxy-2,11,15-trihydroxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c: 2,1-/] [1,4,7,10,13,16]-hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.
Partial ^{1}H NMR : 7.28-7.45 (m, 5H, -OCH_2Ph), 7.18 (dd, 1H, 8.64 hz & 1.86 hz, Ar-H), 7.06 (d, 1H, 1.86 hz, Ar-H), 6.8 (d, 1H, 8.64 hz, Ar-H), 5.02 (d, 1H, 1.86 hz), 4.68 (s, 2H, -OCH_2Ph), 3.78 (s, 2H), 2.89-3.28 (m, 9H), 1.7-1.9 (m, 10H).
IR(KBr): 3300-3400 br, 2940, 1660 br, 1635, 1518, 1460, 1370 br, 1075 cm^{-1}
ESI MS(ES+): for $C_{66}H_{103}N_9O_{16}$
Calculated : 1278.584
Found :$(M+Na)^+$ = 1300.5
1132.4 (base peak), 1102.7, 1024, 567.2.
UV(MeOH): λ_{max} : 208, 225, 279 nm (ε = 46029, 13780, 1619)

Compound 27 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-benzyloxy-23-((1S,2S)-1,2-dihydroxy-2-(3-(4-(2,6-dimethylphenyl)-1,4-diazinan-1-ylmethyl)-4-

hydroxyphenyl)ethyl)-2,11,15-trihydro- xy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodi- azolo [2,1-c:2,1-*f*] [1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^{1}H NMR : 7.29-7.42 (m, 5H, -OCH_2Ph), 7.18 (dd, 1H, 8.55 hz & 1.32 hz, Ar-H), 7.09 (d, 1H, 1.32 hz, Ar-H), 6.9-7.03 (m, 3H, Ar-H), 6.81 (d, 1H, 8.55 hz, Ar-H), 5.31 (br, 1H), 4.68 (s, 2H, -OCH_2Ph), 3.91 (s, 2H), 3.2 (br, 4H), 2.82 (br, 4H), 2.38 (s, 6H, 2 x Ar-CH_3).

^{13}C NMR Spectrum :

176.82, 174.95, 174.20, 174.03, 173.53, 172.67, 170.63, 159.28, 149.74, 140.71, 138.70, 133.76, 130.98, 130.84, 130.06, 129.64, 129.36, 127.85, 127.35, 122.66, 117.51, 81.42, 77.57, 76.79, 76.54, 72.22, 71.04, 70.74, 69.04, 64.16, 63.24, 62.09, 59.25, 57.91, 56.32, 55.62, 54.98, 54.73, 53.59, 51.94, 51.11, 39.81, 39.45, 38.56, 37.61, 36.46, 35.93, 31.89, 31.58, 31.47, 31.36, 31.11, 28.99, 27.85, 20.65, 20.51, 20.46, 12.56, 11.98.

IR(KBr): 3300-3400 br, 2935, 1660 br, 1625, 1530, 1450, 1385, 1260, 1070 cm^{-1}

ESI MS(ES+): for $C_{68}H_{101}N_9O_{16}$

Calculated : 1300.590

Found :$(M+Na)^+$ = 1322.5

1132.5 (base peak), 567.2.

UV(MeOH): λ_{max} : 208, 226, 267 nm (ε = 37979, 14394, 2709)

Compound 28 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-benzyloxy-23-((1S,2S)-1,2-dihydroxy-2-(3,5-di(4-(2,6-dimethylphenyl)-1,4-diazinan-1-ylmethyl)-4-hydroxyphenyl)ethyl)-2,11,15-trihy- droxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhy- drodiazolo[2,1-c:2,1-*f*] [1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^{1}H NMR : 7.28-7.42 (m, 5H, -OCH_2Ph), 7.21 (s, 2H, Ar-H), 6.98-7.2 (m, 6H, Ar-H), 5.33 (br, 1H), 4.68 (s, 2H, -OCH_2Ph), 4.11 (s, 4H), 3.29 (br, 8H), 3.05 (br, 8H), 2.40 (s, 12H, 4 x Ar-CH_3).

IR(KBr): 3350-3450 br, 2920, 1670 br, 1630, 1535, 1460, 1390(sharp), 1220, 1070 cm^{-1}

ESI MS(ES+): for $C_{81}H_{119}N_{11}O_{16}$

Calculated : 1502.889

Found :$(M+Na)^+$ = 1525.6

1503.7, 1334.6, 1204.6, 1144.6 (base peak), 668.4.

UV(MeOH): λ_{max} : 211, 226, 257, 282 nm (ε = 58787, 26424, 8513, 5187)

Compound 29 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-benzyloxy-23-((1S,2S)-1,2-dihydroxy-2-(4-hydroxy-3-(4-(1-phenylethyl)-1,4-diazinan-1-ylmethyl)phenyl)ethyl)-2,11,15-trihydroxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo- [2,1-c:2,1-*f*] [1,4,7,10,13,16] hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^{1}H NMR : 7.28-7.45 (m,10H, -OCH_2Ph & -$CH(CH_3)$Ph), 7.17 (dd, 1H, 8.55 hz & 1.32 hz, Ar-H), 7.03 (d, 1H, 1.32 hz, Ar-H), 6.77 (d, 1H, 8.55 hz, Ar-H), 5.31 (d, 1H, 1.98 hz), 4.68 (s, 2H, -OCH_2Ph), 3.75 (s, 2H), 3.8 (q, 1H, 7.89 hz), 2.6-2.79 (m, 8H), 1.45 (d, 3H, 7.89 hz).

^{13}C NMR Spectrum :

176.80, 174.92, 174.08, 173.50, 172.66, 170.65, 159.20, 144.93, 144.51, 140.70, 133.68, 130.41, 130.18, 130.05, 129.63, 129.34, 129.15, 129.08, 123.63, 117.41, 81.43, 77.49, 76.81, 76.55, 72.18, 72.12, 71.02, 70.66, 69.01, 67.13, 64.13, 63.19, 62.09, 59.21, 57.85, 56.43, 54.68, 54.29, 53.58, 52.38, 51.93, 51.41, 50.99, 46.62, 39.80, 39.41, 38.54, 37.60, 36.43, 35.95, 31.87, 31.55, 31.45, 31.36, 31.10, 28.96, 27.83, 20.94, 20.45, 12.56, 11.98.

IR(KBr): 3300-3400 br, 2920, 1660 br, 1625, 1530, 1455, 1390(sharp), 1260, 1070 cm^{-1}

ESI MS(ES+): for $C_{68}H_{101}N_9O_{16}$

Calculated : 1300.590

Found :$(M+Na)^+$ = 1323.6

1300.6, 1132.5, 808.5, 567.3.

UV(MeOH): λ_{max} : 206, 223, 279 nm (ε = 47065, 14834, 1881)

Compound 30 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-benzyloxy-23-((1S,2S)-1,2-dihydroxy-2-(3,5-di(4-(1-phenylethyl)-1,4-diazinan-1-ylmethyl)-4-hydroxyphenyl) ethyl)-2,11,15-trihydroxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodi- azolo [2,1-c:2,1-*f*] [1,4,7,10,13,16]-hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^{1}H NMR : 7.22-7.40 (m, 15H, -OCH_2Ph & 2 x -$CH(CH_3)$Ph), 6.84 (s, 2H, Ar-H), 5.02 (br, 1H), 4.45 (s, 2H, -OCH_2Ph), 3.52 (s, 4H), 3.42 (q, 2H, 7.8 hz), 2.3-2.55 (m, 16H), 1.28 (d, 6H, 7.8 hz).

IR(KBr): 3300-3450 br, 2920,1655,1625,1525,1450, 1385(sharp), 1255, 1070 cm^{-1}

ESI MS(ES+): for $C_{81}H_{119}N_{11}O_{16}$

Calculated : 1502.889

Found :$(M+ Na)^+$ = 1525.7

1502.8, 1334.6, 1204.6, 1144.4, 763.5, 668.0, 567.0.

UV(MeOH): λ_{max} : 205, 219, 284 nm (ε = 50300, 7314, 1833)

Compound 31 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-23-((1S,2S)-2-(3-benzyl(tert.butyl)amino- methyl-4-hydroxyphenyl)-1,2-dihydroxyethyl)-12-benzyloxy-2,11,15-trihydroxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhyd-rodiazolo[2,1-c:2,1-*f*] [1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^{1}H NMR : 7.15-7.45 (m, 10H, -OCH_2Ph & -NCH_2Ph), 7.05 (dd, 1H, 8.37 hz & 1.41 hz, Ar-H), 6.95 (d, 1H, 1.41 hz, Ar-H), 6.55 (d, 1H, 8.37 hz, Ar-H), 5.32 (d, 1H, 2.1 hz), 4.68 (s, 2H,-OCH_2Ph), 4.09 (s, 2H), 3.89 (s, 2H), 1.42 (s, 9H, 3 x e or -$C(CH_3)_3$).

IR(KBr): 3300-3400 br, 2920, 1660 br, 1625, 1525, 1440, 1375(sharp), 1250, 1070 cm^{-1}

ESI MS(ES+): for $C_{67}H_{100}N_8O_{16}$

Calculated : 1273.565

Found :$(M+Na)^+$ = 1296.6

1132.5 (base peak), 567.3.

UV(MeOH): λ_{max} : 210, 226, 280 nm (ε = 76304, 28418, 4257)

Compound 32 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-23-((1S,2S)-2-(3-benzyl(isopropyl)amino- methyl-4-hydroxyphenyl)-1,2-dihydroxyethyl)-12-benzyloxy-2,11,15-trihydroxy-6-((1R)-1-hy- droxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhyd-rodiazolo[2,1-c:2,1-/][1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^{1}H NMR : 7.28-7.45 (m, 10H, -OCH$_2$Ph & -NCH$_2$Ph), 7.16 (dd, 1H, 8.55 hz & 1.98 hz, Ar-H), 7.05 (d, 1H, 1.98 hz, Ar-H), 6.74 (d, 1H, 8.55 hz, Ar-H), 5.32 (br, 1H), 4.68 (s, 2H, OCH$_2$Ph), 3.9, 3.65 (2 x s, 4H), 3.1 (m, 1H), 1.22 (m, 6H).

IR(KBr): 3300-3400 br, 2935, 1680-1625 br, 1540, 1450, 1385(sharp), 1260, 1075 cm^{-1}

ESI MS(ES+): for $C_{66}H_{98}N_8O_{16}$

Calculated : 1259.538

Found :(M+Na)$^+$ = 12.81.8

1132.4 (base peak), 567.1.

UV(MeOH): λ_{max} : 207, 231, 280 nm (ε = 58232, 10790, 2997)

Compound 33 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-benzyloxy-23-((1S,2S)-2-(3,5-di(benzyl(iso-propyl)aminomethyl-4-hydroxyphenyl)-1,2-dihydroxyethyl)-12-benzyloxy-2,11,15-trihydroxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c:2,1-/][1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^{1}H NMR : 7.28-7.43 (m, 15H, -OCH$_2$Ph & 2 x -NCH$_2$Ph), 7.03 (s, 2H, Ar-H), 5.33 (br, 1H), 4.68 (s, 2H, -OCH$_2$Ph), 3.87, 3.63 (2 x s, 8H), 3.0 (m, 2H), 1.2-1.3 (m, 12H).

IR(KBr): 3400-3500 br, 2945, 1680- 1630 br, 1540, 1460, 1385(sharp), 1260, 1080 cm^{-1}

ESI MS(ES+): for $C_{77}H_{113}N_9O_{16}$

Calculated : 1420.784

Found :$(M)^+$ = 1420.9

1293.4, 1144.9(base peak), 1024.4, 996.2, 648.1.

UV(MeOH): λ_{max} pH: 207, 227, 282 nm (ε = 67687, 10661, 1465)

Compound 34 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-23-((1S)-2-(3-(1-azinanylmethyl)-4-hydro- xyphenyl)-2-benzyloxy-1-hydroxyethyl)-12-benzyloxy-2,11,15-trihydroxy-6-((1R)-1-hydroxy- thyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c:2,1-/] [1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^{1}H NMR : 7.25-7.41 (m, 10H, 2 x OCH_2Ph), 7.2 (dd, 1H, 8.5 hz & 1.85 hz, Ar-H), 7.14 (d, 1H, 1.85 hz, Ar-H), 6.87 (d, 1H, 8.5 hz), 5.35 (br, 1H), 4.6 (s, 4H, 2 x -OCH_2Ph), 4.14 (s, 2H), 3.12 (m, 4H), 2.04 (m, 6H).

IR(KBr): 3300-3400 br, 2915, 1650, 1620, 1530, 1440, 1250, 1070 cm^{-1}

ESI MS(ES) : for $C_{68}H_{100}N_8O_{16}$

Calculated : 1285.576

Found : $(M+Na)^+$ = 1308.6(base peak), 567.3

UV(MeOH):- λ_{max} : 211, 255, 288 nm (ε = 73984, 20087, 5142)

Compound 35 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-benzyloxy-23-((1S)-2-benzyloxy-2-(3,5-di(1-azinanylmethyl)-4-hydroxyphenyl)-1-hydroxyethyl)-2,11,15-trihydroxy-6-(1R)-1-hydroxy- ethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c:2,1-/] [1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^{1}H NMR : 7.28-7.45 (m, 10H, 2 x -OCH_2Ph), 7.21 (2 x s, 2H, Ar-H), 5.32 (br, 1H), 4.65 (s, 4H, 2 x -OCH_2Ph), 4.11 (m, 4H), 2.98 (m, 8H), 1.98 (m, 12H).

IR(KBr): 3300-3400 br, 2910, 1650, 1625 br,1530, 1440, 1250, 1070 cm^{-1}

ESI MS(ES+): for $C_{74}H_{111}N_9O_{16}$

Calculated : 1382.735

Found :$(M+Na)^+$ = 1404.8 (base peak)

1382.6, 1320.7, 1189.4, 1081.6, 808.5, 567.3.

UV(MeOH): λ_{max} : 209, 234, 290 nm (ε = 46021, 9127, 3989)

Compound 36:

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-23-((1S)-2-(3-(1-azolanylmethyl)-4-hydro- xyphenyl)-2-benzyloxy-1-hydroxyethyl)-12-benzyloxy-2,11,15-trihydroxy-6-((1R)-1-hydroxy- ethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c:2,1-/] [1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^{1}H NMR : 7.25-7.41 (m, 10H, 2 x -OCH_2Ph), 7.25 (dd, 1H, 8.5 hz & 1.9 hz, Ar-H), 7.14 (d, 1H, 1.9 hz, Ar-H), 6.87 (d, 1H, 8.5 hz, Ar-H),5.31 (br, 1H),4.67(s, 4H, 2 x-OCH_2Ph), 4.13 (s, 2H), 3.35 (m, 4H), 2.1 (m, 4H).

IR(KBr): 3300-3400 br, 2925, 1650, 1620, 1535, 1450, 1250, 1075 cm^{-1}

ESI MS(ES+): for $C_{67}H_{98}N_8O_{16}$

Calculated : 1271.549

Found :$(M+Na)^+$ = 1293.6 (base peak)

1159.0, 1114.5, 734.9.

UV(MeOH): λ_{max} : 211, 230, 278 nm (ε = 64015, 27056, 6845)

Compound 37:

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-benzyloxy-23-((1S)-2-benzyloxy-2-(3,5-di(1-azolanylmethyl)-4-hydroxyphenyl)-1-hydroxyethyl)-2,11,15-trihydroxy-6-((1R)-1-hydroxy ethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c:2,1-/] [1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^{1}H NMR : 7.28-7.41 (m, 10H, 2 x -OCH_2Ph), 7.10, 7.14 (2 x s, 2H, Ar-H), 5.33 (br, 1H), 4.68 (s, 4H, 2 x -OCH_2Ph), 4.18 (m, 4H), 3.12 (m, 8H), 2.05 (m, 8H).

IR(KBr): 3320-3420 br, 2920, 1660-1630 br, 1530, 1465, 1080 cm^{-1}

ESI MS(ES+): for $C_{72}H_{107}N_9O_{16}$

Calculated : 1354.682

Found :$(M+Na)^+$ = 1376.6 (base peak)

1354.5, 1305.6, 1175.7, 1067.5, 653.8.

UV(MeOH): λ_{max} : 208, 230, 289 nm (ε = 64738, 12888, 5155)

Compound 38:

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-benzyloxy-23-((1S)-2-benzyloxy-1-hyd- roxy-2-(4-hydroxy-3-(4-methyl-1-azinanylmethyl) phenyl) ethyl)-2,11,15-trihydroxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo-[2,1-:2,1-/][1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^{1}H NMR : 7.2-7.41 (m, 10H, 2 x -OCH_2Ph), 7.17 (dd, 1H, 8.32 hz & 1.8 hz, , Ar-H), 7.0 (d, 1H, 1.8 hz, Ar-H), 6.78 (d, 1H, 8.32 hz, Ar-H), 5.31 (br, 1H), 4.68 (s, 4H, 2 x -OCH_2Ph), 4.1 (s, 2H), 2.65 (m, 4H), 1.85 (m, 4H), 1.28 (m,1H), 1.06 (m, 3H, $CHCH_3$).

IR(KBr)(acetate salt) :-3330-3400 br, 2950, 1717, 1635, 1530, 1450, 1250, 1065, 1065 cm^{-1}

ESI MS(ES+): for $C_{69}H_{102}N_8O_{16}$

Calculated : 1299.602

Found :$(M+Na)^+$ = 1321.7 (base peak), 559.47.

UV(MeOH): λ_{max} : 208, 230, 284 nm (ε = 49233, 17260, 3249)

Compound 39:

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-benzyloxy-23-((1S)-2-benzyloxy-1-hydroxy-2-(4-hydroxy-3,5-di(4-methyl-1-azinanylmethyl)phenyl)ethyl)-2,11,15-trihydroxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodia-zolo [2,1-c:2,1-/][1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^{1}H NMR : 7.25-7.41 (m, 10H, 2 x -OCH_2Ph), 7.09, 7.21 (2 x s, 2H, Ar-H), 5.33 (br, 1H), 4.68 (s, 4H, 2 x OCH_2Ph), 4.11 (s, 4H), 2.7 (m, 8H), 1.85 (m, 8H), 1.25 (m, 2H), 1.06 (m, 6H).

IR(KBr)(915/78.D,acetate salt): 3350-3450 br, 2960, 1715(sharp), 1635, 1530, 1455, 1060 cm^{-1}

ESI MS(ES+): for $C_{76}H_{115}N_9O_{16}$

Calculated : 1430.659

Found :$(M+Na)^+$ = 1432.9
1411.6, 1333.6, 1203.7, 1095.7, 808.3, 559.4, 667.6.
UV(MeOH): λ_{max} : 206, 237, 288 nm (ε = 1463, 153, 29)

Compound 40 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-benzyloxy-23-((1S)-2-benzyloxy-1-hydroxy-2-(4-hydroxy-3-(4-(3-trifluromethylphenyl)-1,4-diazinan-1-ylmethyl)phenyl)ethyl)-2,11,15-trihydroxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c:2,1-*f*][1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyl-tetradecanamide.

Partial ^{1}H NMR : 7.28-7.5 (m, 10H, 2 x -OCH_2Ph), 7.15-7.27 (m, 4H, Ar-H), 7.12 (dd, 1H, 8.22 hz, & 1.38 hz), 7.05 (d, 1H, 1.38 hz, Ar-H), 6.85 (d, 1H, 8.22 hz , Ar-H), 5.32 (br, 1H), 4.68 (s, 4H, 2 x -OCH_2Ph), 3.85 (s, 2H), 2.81 (m, 8H).

IR(KBr): 3300-3400 br, 2910, 2330(sharp), 1640 br, 1610, 1515, 1430, 1300, 1220, 1065 cm^{-1}

ESI MS(ES+): for $C_{74}H_{102}F_3N_9O_{16}$

Calculated : 1430.659

Found :$(M+Na)^+$ = 1452.7
1222.2 (base peak), 567.3.

Compound 41 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-benzyloxy-23-((1S)-2-benzyloxy-1-hydroxy-2-(4-hydroxy-3,5-di(4-(3-trifluromethylphenyl)-1,4-diazinan-1-ylmethyl)phenyl)- ethyl)-2,11,15-trihydroxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14, 19,22,25-hexaoxoperhydrodiazolo[2,1-c:2,1-*f*][1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^{1}H NMR : 7.25-7.45 (m, 10H, 2 x -OCH_2Ph), 7.02-7.2 (m,10H, Ar-H), 5.33 (br, 1H), 4.68 (s, 4H, 2 x -OCH_2Ph), 3.8 (s, 4H), 2.75-2.9 (m, 16H).

IR(KBr): 3300-3400 br, 2925, 1660 br, 1610, 1540, 1455, 1330, 1260, 1075 cm^{-1}

ESI MS(ES+): for $C_{86}H_{115}F_6N_{11}O_{16}$

Calculated : 1672.903

Found :$(M+Na)^+$ = 1695.5

1222.6, 567.1.

UV(MeOH): λ_{max} : 212, 255, 282, 305 nm (ε = 41827, 20244, 4567, 2018)

Compound 42 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-benzyloxy-23-((1S)-2-benzyloxy-2-(3-dibenzylaminomethyl-4-hydroxyphenyl)-1-hydroxyethyl)-2,11,15-trihydroxy-6-((1R)-1-hydro- xyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c:2,1-/] [1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^{1}H NMR : 7.22-7.44 (m, 20H, 2 x -OCH_2Ph & -$N(CH_2Ph)_2$), 7.11 (dd, 1H, 8.6 hz & 2.2 hz, Ar-H), 7.08 (d, 1H, 2.2 hz, Ar-H), 6.81 (d, 1H, 8.6 hz, Ar-H), 5.3 (br, 1H), 4.68 (s, 4H, 2 x -OCH_2Ph), 3.6-3.7 (s, 4H), 3.79 (s, 2H).

IR(KBr): 3300-3400 br, 2930, 1650 br, 1615(sharp), 1516, 1435, 1240, 1060 cm^{-1}

ESIMS(ES+): for $C_{77}H_{104}N_8O_{16}$

Calculated : 1397.706

Found : $(M+Na)^+$ = 1421.6

1222.8 (base peak), 1114.1, 768.8, 567.2.

UV(MeOH): λ_{max} : 210, 228, 280 nm (ε = 61484, 15835, 2697)

Compound 43 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-23-((1S,2S)-1,2-dihydroxy-2-(3-(4-(4-fluorophenyl)-1,4-diazinan-1-ylmethyl)-4-hydroxyphenyl)ethyl)-2,11,15-trihydroxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-12-methoxy-16-methyl-5,8,14,19,22,25-hexaoxoperhydro- diazolo[2,1-c:2,1-/]

[1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^{1}H NMR : 7.18 (dd, 1H, 8.40 hz & 1.53 hz), 7.08 (d, 1H, 1.53 hz, Ar-H), 7.02 (d, 4H, 8.25 hz, Ar-H), 6.8 (d, 1H, 8.40 hz, Ar-H), 5.12 (d, 1H, 1.5 hz), 3.83 (s, 2H), 3.38 (s , 3H, OCH_3), 3.2 (br, 4H), 2.79 (br, 4H).

IR(KBr): 3300-3400br, 2930, 1645, 1620, 1510, 1440, 1380, 1230, 1070 cm^{-1}

ESI MS(ES+): for $C_{60}H_{92}FN_9O_{16}$

Calculated : 1214.429

Found : $M+Na)^+$ = 1236.7

1124.5, 1056.4 (base peak), 1012.4, 808.4, 567.2.

UV(MeOH): λ_{max} : 205, 230, 282 nm (ε = 35278, 16251, 1477)

Compound 44 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-23-((1S,2S)-2-(3,5-di(4-(4-fluorophenyl)-1,4-diazinan-1-ylmethyl)-4-hydroxyphenyl)-1,2-dihydroxyethyl)-2,11,15-trihydroxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-12-methoxy-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodia- zolo[2,1-c:2,1-*f*] [1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide

Partial ^{1}H NMR : 7.13 (s, 2H, Ar-H), 7.0-7.1(m, 8H, Ar-H), 5.12 (br, 1H), 3.82 (s, 4H), 3.38 (s, 3H, OCH_3), 3.21 (br, 8H), 2.78 (br, 8H).

IR(KBr): 3300-3400br, 2930, 1645, 1620, 1510, 1440, 1380, 1230, 1070 cm^{-1}

ESI MS(ES+): for $C_{71}H_{105}F_2N_{11}O_{16}$

Calculated : 1406.665

Found :$(M+Na)^+$ = 1428.9

1249.6, 1068.4 (base peak), 839.8, 567.1.

UV(MeOH): λ_{max} : 207, 215, 234, 284 nm (ε = 46370, 30669, 14068, 2900)

Compound 45 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-23-((1S,2S)-1,2-dihydroxy-2-(4-hydroxy-3-(4-phenyl-1,4-diazinan-1-ylmethyl)phenyl)ethyl)-2,11,15-trihydroxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-12-methoxy-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c:2,1-*f*] [1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^{1}H NMR : 7.22-7.35 (m, 2H, Ar-H), 7.2 (dd, 1H, 8.22 hz & 1.98 hz, Ar-H), 7.1 (d, 1H, 1.98 hz, Ar-H), 7.02 (m, 2H, Ar-H), 6.9 (m, 1H, Ar-H), 6.81 (d, 1H, 8.22 hz, Ar-H), 5.13 (d, 1H, 1.5 hz), 3.9 (s, 2H), 3.42 (s, 3H, OCH_3), 3.2-3.3 (br, 4H), 2.85-2.95 (br, 4H).

IR(KBr): 3350-3450 br, 2920, 1650 br, 1620, 1530, 1435, 1375, 1220, 1070 cm^{-1}

ESI MS(ES+): for $C_{60}H_{93}N_9O_{16}$

Calculated : 1196.439

Found :$(M+Na)^+$ = 1218.2

1056.4(base peak),1025.1, 893.0, 567.3.

UV(MeOH): λ_{max} : 207, 232, 248, 279 nm (ε = 44536, 15767, 15368, 3562)

Compound 46 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-23-((1S,2S)-1,2-dihydroxy-2-(3,5-di(4-phenyl-1,4-diazinan-1-ylmethyl)-4-hydroxyphenyl)ethyl)-2,11,15-trihydroxy-6-((1R)-1-hydroxy ethyl)-20-hydroxymethyl-12-methoxy-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c:2,1-/][1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide

Partial ^{1}H NMR : 7.24-7.41 (m, 4H, Ar-H), 7.15 (s, 2H, Ar-H), 7.0 (m, 4H, Ar-H), 6.89 (m, 2H, Ar-H), 5.1 (br, 1H), 3.83 (s, 4H), 3.4 (s, 3H, CH_3), 3.12-3.21 (br, 8H), 2.68-2.95 (br, 8H).

IR(KBr): 3350-3450 br, 2920, 1650 br, 1620, 1530, 1435, 1375, 1220, 1070 cm^{-1}

ESI MS(ES+): for $C_{71}H_{107}N_{11}O_{16}$

Calculated : 1370.684

Found :$(M+Na)^+$ = 1393.0

1232.5, 1054.3 (base peak), 1042.0.

UV(MeOH): λ_{max} : 205, 248, 279 nm (ε = 29408, 8099, 1557)

Compound 47 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-benzyloxy-23-((1S)-2-(1H-1,3-diazol-1-yl)-2-(3-(1H-1,3-diazol-1-ylmethyl)-4-hydroxyphenyl)-1-hydroxyethyl)-2,11,15-trihydroxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-ethyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo- [2,1-c:2,1-/][1,4,7,10,13,16] hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide

To a stirred solution of ornithine-5-benzylmulundocandin 2 (0.2 g, 0.182 mmol) in anhydrous N,N-dimethylformamide (10 ml) was added imidazole (0.122 g, 1.8 mmol), paraformaldehyde (0.108 g, 3.6 mmol) and heated under reflux for 15 hr. Reaction progress was monitored by TLC (20 % MeOH/$CHCl_3$). The reaction work-up and purification procedure was similar to that of compound 6. Yield of the white solid 47 (0.03 g, 13.42 %).

Partial ^1H NMR : 7.8-7.7 (m, 2H, Ar-H), 7.42-7.28 (m, 5H, OCH_2Ph), 6.99-7.1, 7.19 (2 x br, 6Hv), 6.82 (d, 1H, 8.13 hz, Ar-H), 5.32 (s,1H), 4.67 (s , 2H, OCH_2Ph), 3.8 (s, 2H).

ESI MS(ES+): for $C_{62}H_{89}N_{11}O_{16}$

Calculated : 1228.444

Found : $(M+Na)^+$ = 1250.41130.4, 1063.6, 950.8, 805.7, 357.9, 259.1, 229.2(base peak).

UV(MeOH): λ_{max} : 210, 271 nm (ε = 53232, 2538)

TABLE III

Comp. No.	Starting Compound	Secondary Amine	Para-formal-dehyde	Dioxan (ml)/ React. time (hr.)	Comp.No. Yield (g , %)	M.P.(°C)	Mole.Formula/ Mole.Weight.
7&8	Orn-5-benzyl MLD(2) 0.1 g, 0.091 mmol	Pyrrolidin 0.0647 g, 0.91 mmol	0.0546 g, 1.82 mmol	10/4	7 0.025 g, 23.24 8 0.023 g, 19.98	7 145 (dec) 8 NA	7 $C_{60}H_{92}N_9O_{16}$ 1181.424 8 $C_{65}H_{101}N_9O_{16}$ 1264.557
9&10	2 0.2 g, 0.182 mmol	1-(2-Flurophenyl), piperazine 0.328 g, 1.82 mmol	0.109 g, 3.64 mmol	10/6	9 0.083 g, 35.31 10 0.105 g, 38.88	9 169 10 145	9 $C_{66}H_{96}FN_9O_{16}$ 1290.527 10 $C_{77}H_{109}F_2N_{11}O_{16}$ 1482.763
11&12	2 0.3 g, 0.273 mmol	1-(2-Chlorophenyl), piperazine 0.536 g, 2.73 mmol	0.163 g, 5.46 mmol	15/5	11 0.16 g, 44.81 12 0.074 g, 17.87	11 105 12 109-110	11 $C_{66}H_{96}Cl\ N_9O_{16}$ 1306.982 12 $C_{77}H_{109}Cl_2N_{11}O_{16}$ 1515.672

Comp. No.	Starting Compound	Secondary Amine	Para-formal-dehyde	Dioxan (ml)/ React. time (hr.)	Comp.No. Yield (g , %)	M.P.(°C)	Mole.Formula/ Mole.Weight.
13	2 0.2 g, 0.182 mmol	N-(α,α,α-Trifluro -m-tolyl) piperazine 0.419 g, 1.8 mmol	0.109 g, 3.64 mmol	10/5	13 0.165 g, 67.59	13 111	13 $C_{67}H_{96}F_3N_9O_{16}$ 1340.535
14&15	2 0.25 g, 0.228 mmol	1-(2-Pyrimidyl), piperazine 0.347 g, 2.28 mmol	0.136 g, 4.56 mmol	10/5	14 0.078 g, 26.89 15 0.050 g, 15.24	NA NA	14 $C_{64}H_{95}N_{11}O_{16}$ 1274.512 15 $C_{73}H_{107}N_{15}O_{15}$ 1450.773
16&17	2 0.3 g, 0.273 mmol	1-(4-Flurophenyl), piperazine 0.492 g, 2.73 mmol	0.163 g, 5.46 mmol	15/5	16 0.22 g, 62.41 17 0.086 g, 21.23	16 161 (dec) 17 103	16 $C_{66}H_{96}FN_9O_{16}$ 1290.527 17 $C_{77}H_{109}F_2N_{11}O_{16}$ 1482.763
18&19	2 0.25 g, 0.228 mmol	1-Phenyl piperazine 0.369 g, 2.28 mmol	0.136 g, 4.56 mmol	10/16	18 0.11 g, 37.98 19 0.1 g, 30.39	18 164 19 134	18 $C_{66}H_{97}N_9O_{15}$ 1272.537 19 $C_{77}H_{111}N_{11}O_{16}$ 1446.782
20	2 0.25 g, 0.228 mmol	Dibenzylamine 0.449 g, 2.28 mmol	0.136 g, 4.56 mmol	10/24	20 0.17 g, 57.12	20 160-161	20 $C_{70}H_{98}N_8O_{15}$ 1307.582
21	2 0.25 g, 0.228 mmol	1-Benzyl piperazine 0.401 g, 2.28mmol	0.136 g, 4.56 mmol	10/18	21 0.18 g, 61.47	21 154	21 $C_{67}H_{99}N_9O_{16}$ 1286.563
22	2 0.194g , 0.177 mmol	1-(2-Pyridyl) piperazine 0.288 g , 1.77	0.106 g, 3.54 mmol	10/6	22 0.14 g, 62.24	22 159-161	22 $C_{65}H_{96}N_{10}O_{16}$ 1273.524

Comp. No.	Starting Compound	Secondary Amine	Para-formal-dehyde	Dioxan (ml)/ React. time (hr.)	Comp.No. Yield (g , %)	M.P.(°C)	Mole.Formula/ Mole.Weight.
23&24	2 0.4 g, 0.364 mmol	1-(4-Methylphenyl) piperazine 0.288 g, 1.77 mmol	0.218 g, 7.28 mmol	15/20	23 0.19 g, 40.55 24 0.034 g, 6.33	23 140 24 166	23 $C_{67}H_{99}N_9O_{16}$ 1286.583 24 $C_{79}H_{115}N_{11}O_{16}$ 1474.835
25	2 0.3 g, 0.273 mmol	1-(4-Pyridyl) piperazine 0.445 g , 2.73 mmol	0.163 g, 5.46 mmol	15/7	25 0.207 g, 52.31	25 89	25 $C_{75}H_{109}N_{13}O_{16}$ 1448.457
26	2 0.35 g, 0.319 mmol	4 –Piperidino-piperidine 0.536 g, 3.19 mmol	0.191 g, 6.38 mmol	15/2.5	26 0.27 g, 66.33	26 87	26 $C_{66}H_{103}N_9O_{16}$ 1278.584
27&28	2 0.325 g, 0.296 mmol	1-(2,6-Dimethyl phenyl) piperazine 0.563 g, 2.96 mmol	0.177 g, 5.92 mmol	15/6	27 0.17 g, 44.17 28 g , 17.53	27 165 28 136	27 $C_{68}H_{101}N_9O_{16}$ 1300.590 28 $C_{81}H_{119}N_{11}O_{16}$ 1502.889
29&30	2 0.35 g, 0.319 mmol	1-(1-Phenylethyl) piperazine 0.607 g, 3.19 mmol	0.191 g, 6.38 mmol	15/8	29 0.13 g, 31.37 30 0.205 g, 42.80	29 142 30 110	29 $C_{68}H_{101}N_9O_{16}$ 1300.590 30 $C_{81}H_{119}N_{11}O_{16}$ 1502.889
31	2 0.35 g, 0.319 mmol	N-(ter.butyl) benzylamine 0.52 g, 3.19 mmol	0.191 g, 6.38 mmol	15/24	31 0.03 g, 7.39	NA	31 $C_{67}H_{100}N_8O_{16}$ 1273.565

Comp. No.	Starting Compound	Secondary Amine	Para-formal-dehyde	Dioxan (ml)/ React. time (hr.)	Comp.No. Yield (g , %)	M.P.(°C)	Mole.Formula/ Mole.Weight.
32&33	2 0.35 g, 0.319 mmol	N-(Isopropyl) benzylamine 0.476 g, 3.19 mmol	0.191 g , 6.38 mmol	15/6	32 0.13 g, 32.39 33 0.125 g, 27.61	32 145 33 103-105	32 $C_{66}H_{98}N_8O_{16}$ 1259.538 33 $C_{77}H_{113}N_9O_{16}$ 1420.784
34&35	Orn-5 & homo-Tyr-4-dibenzyl , MLD(3) 0.35 g, 0.294 mmol	Piperidine 0.250 g , 2.94 mmol	0.176 g , 5.88 mmol	30/31	34 0.17 g, 19.64 35 0.25 g, 26.88	34 NA 35 76-80	34 $C_{68}H_{100}N_8O_{16}$ 1285.576 35 $C_{74}H_{111}N_9O_{16}$ 1382.735
36&37	3 0.1 g, 0.084 mmol	Pyrrolidin 0.059 g , 0.84 mmol	0.0504 g , 1.68 mmol	10/3	36 0.021 g, 19.64 37 0.05 g, 43.89	36 NA 37 81-83	36 $C_{67}H_{98}N_8O_{16}$ 1271.549 37 $C_{72}H_{107}N_9O_{16}$ 1354.682
38&39	3 0.322 g, 0.271 mmol	4 –Methyl piperidine 0.268 g , 2.71 mmol	0.162 g , 5.42 mmol	15/16	38 0.09 g, 25.56 39 0.087 g, 22.76	38 135-137 39 87-90	38 $C_{69}H_{102}N_8O_{16}$ 1299.602 39 $C_{75}H_{115}N_9O_{16}$ 1410.789
40&41	3 0.422 g, 0.355 mmol	N-(α,α,α-Trifluro-m-tolyl) piperazine 0.817 g , 3.55 mmol	0.213 g , 7.1 mmol	20/6	40 0.04 g, 7.87 41 0.35 g, 58.92	40 155-160 41 172-173	40 $C_{74}H_{102}F_3N_9O_{16}$ 1430.659 41 $C_{86}H_{115}F_6N_{11}O_{16}$ 1672.903
42	3 0.25 g, 0.21 mmol	Dibenzylamine 0.414 g , 2.1 mmol	0.213 g , 7.1 mmol	15/18	42 0.130 g, 44.12	42 149-151	42 $C_{77}H_{104}N_8O_{16}$ 1397.706

Comp. No.	Starting Compound	Secondary Amine	Para-formal-dehyde	Dioxan (ml)/ React. time (hr.)	Comp.No. Yield (g , %)	M.P.(°C)	Mole.Formula/ Mole.Weight.
43&44	Orn-5-methoxy , MLD(4) 0.3 g, 0.293 mmol	1-(4-Flurophenyl) piperazine 0.528 g, 2.93 mmol	0.175 g , 5.86 mmol	15/5	43 0.19 g, 53.31 44 0.071 g, 16.99	43 191-192 44 110	43 $C_{60}H_{92}FN_9O_{16}$ 1214.429 44 $C_{71}H_{105}F_2N_{11}O_{16}$ 1406.665
45&46	4 0.4 g, 0.391 mmol	1-Phenyl piperazine 0.634 g , 3.91 mmol	0.234 g , 7.82 mmol	20/6	45 0.23 g, 49.13 46 0.05 g, 9.3	45 114 46 NA	45 $C_{60}H_{93}N_9O_{16}$ 1196.439 46 $C_{71}H_{107}N_{11}O_{16}$ 1370.684

(NA = Not Available)
(MLD = mulundocandin)

Procedure for the preparation of compounds 49 & 50:

To a stirred solution of mulundocandin 1 (4.8 g, 5.15 mmol) in anhydrous 1,4-dioxane (150 ml), under nitrogen atmosphere was added anhydrous methylthioglycolate (11.87 g, 111.83 mmol) and a catalytic amount of p-toluenesulfonic acid (0.338 g, 1.758 mmol) and the reaction mixture was stirred at ambient temperature for 1.5 hr. Reaction progress was monitored by TLC (20 % MeOH/$CHCl_3$). TLC analysis after 1.5 hr. showed no starting compound. The reaction was quenched at 5-10 °C by the addition of saturated aqueous $NaHCO_3$ and evaporated to smaller volume (25 ml). The above mixture was diluted with water (250 ml), extracted with n-BuOH (3 x 150 ml), washed with water (200 ml) followed by brine (200 ml). Combined organic extract was dried over anhydrous Na_2SO_4, filtered and was concentrated in vacuum to give gummy product, which was then dissolved in a minimum amount of methanol (MeOH) (15 ml), adsorbed on silica gel (1:1 w/w), and was subjected to silica gel flash column chromatography. 0-15 % MeOH/$CHCl_3$ was used as 5 % step gradient elution. Evaporation of the appropriate fractions gave white compound 49 (3.171 g, 60.75 %) and 49 (0.885 g, 15.69 %).

Compound 49 :

Methyl-2-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-23-((1S,2S)-1,2-dihydroxy-2-(4-hydroxyphenyl)ethyl)-2,11,15-trihydroxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-9-(11-methyltridecylcarboxamido)-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c:1-/][1,4,7,10,13,16]hexaazacyclohenicosin-12-ylsulfanyl] acetate.

Partial ^{1}H NMR : 7.2 (d, 2H, 8.54 hz), 6.8 (d, 2H, 8.54 hz), 5.39 (br, 1H), 3.75 (s, 3H, OCH_3), 3.45, 3.65 (2 x d, 2H, 15.78 hz).

IR(KBr): 3350, 2920, 1730, 1660-1620br, 1520, 1440, 1385, 1230, 1075 cm^{-1}

ESI MS(ES+): for $C_{51}H_{81}N_7O_{17}S$

Calculated : 1096.291

Found :$(M+Na)^+$ = 1118.5 (base peak)

1074.6, 1044.7, 1012.6, 771.3, 589.2, 567.1.

UV(MeOH): λ_{max} pH: 206, 225, 277 nm (ε = 11990, 5769, 9428)

Compound 50 :

Methyl-2-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-2,11,15-trihydroxy-6-((1R)-1-hy- droxyethyl)-23-((1S)-1-hydroxy-2-(4-hydroxyphenyl)-2-methoxycarbonylmethylsulfanyl- ethyl)-20-hydroxymethyl-16-methyl-9-(11-methyltridecylcarboxamido)-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c:1-/][1,4,7,10,13,16]hexaazacyclohenicosin-12-ylsulfanyl]- acetate.

Partial ^{1}H NMR : 7.25, 7.12 (2 x d, 2H, 8.55 hz), 6.8 (2 x d, 2H, 8.55 hz), 5.41 (br, 1H), 3.75 (s, 3H), 3.65, 3.8 (2 x s, 3H), 3.45, 3.64 (2 x d, 2H), 3.21-2.85 (m, 2H).

IR(KBr): 3300-3400 br, 2930, 1740(ester), 1680-1610 br, 1520, 1435, 1380, 1260, 1070 cm^{-1}

ESI MS(ES+): for $C_{54}H_{85}N_7O_{18}S_2$

Calculated : 1184.414

Found :$(M+Na)^+$ = 1206.6 (base peak)

1100.6, 966.5, 859.3, 808.5, 567.2.

UV(MeOH): λ_{max}: 204, 227 nm (ε = 9685, 2421)

Procedure for the preparation of compounds 51 & 52:-

To a stirred solution of mulundocandin 1 (2.3 g, 2.28 mmol) in anhydrous 1,4-dioxane (100 ml), under nitrogen atmosphere was added anhydrous thiophenol

(4.29 g, 38.95 mmol) and a catalytic amount of p-toluenesulfonic acid (0.23 g, 1.196 mmol) and the reaction mixture was stirred at ambient temperature for 3 hr. Reaction progress was monitored by TLC (20 % MeOH/$CHCl_3$). The reaction workup and purification process were similar to that described for compounds 49 and 50. Yield of the white solid 51 (1.241 g, 49.44 %) and 52 (0.478 g, 17.57 %).

Compound 51 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-23-((1S,2S)-1,2-dihydroxy-2-(4-hydro- xyphenyl)ethyl)-2,11,15-trihydroxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl -5,8,14,19,22,25-hexaoxo-12-phenylsulfanyl-perhydrodiazolo[2,1-c:2,1-*f*][1,4,7,10,13,16] hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^1H NMR : 7.58 (m, 2H), 7.33 (t, 3H, 2.63 hz), 7.2 (d, 2H, 8.39 hz), 6.8 (d, 2H, 8.39 hz), 5.69 (br, 1H).

IR(KBr): 3400-3300br, 2940, 1670, 1630, 1525, 1460, 1390, 1250, 1075 cm^{-1}

ESI MS(ES+): for $C_{54}H_{81}N_7O_{15}S$

Calculated : 1100.326

Found :$(M+Na)^+$ = 1122.6 (base peak)

1078.7, 1012.5, 970.6, 808.5, 771.3, 567.3.

UV(MeOH): λ_{max}: 206, 228, 265 nm (ε = 36860, 22336, 4703)

Compound 52 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-2,11,15-trihydroxy-6-((1R)-1-hydroxy- ethyl)-23-((1S)-1-hydroxy-2-(4-hydroxyphenyl)-2-phenylsulfanylethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxo-12-phenylsulfanylperhydrodia-zolo[2,1-c:2,1-*f*] [1,4,7, 10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

Partial ^1H NMR : 7.58 (m, 2H),7.30 (t, 3H, 3.3 hz),7.18-7.25(m, 5H, homo-Tyr-4-SPh), 6.91 (d, 2H, 8.4 hz), 6.61(d, 2H, 8.4 Hz),5.69 (br, 1H).

IR(KBr): 3400-3300 br, 2940, 1680-1620 br, 1520, 1450, 1380, 1240, 1075 cm^{-1}

ESI MS(ES+): for $C_{60}H_{85}N_7O_{14}S_2$

Calculated : 1192.484

Found :$(M+Na)^+$ = 1214.6 (base peak)

1136.7, 466.5.

UV(MeOH): λ_{max}: 205, 255 nm (ε = 32415, 4892)

Compound 53 :

Methyl-2-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-23-((1S,2S)-1,2-dihydroxy-2-(4-hydroxyphenyl)ethyl)-2,11,15-trihydroxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-9-(11-methyltridecylcarboxamido)-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c:1-/][1,4,7,10,13,16]hexaazacyclohenicosin-12-ylsulfonyl] acetate.

To a stirred solution of thioether 48 (0.515 g, 0.47 mmol) in 70 ml of 1:1 acetonitrile/water at ambient temperature was added OXONE® (0.577 g, 0.94 mmol). After a period of 1 hr. TLC analysis (20 % MeOH/$CHCl_3$) showed conversion to a more polar product to be complete. The reaction mixture was evaporated under reduced pressure to smaller volume (25 ml). White solid precipitated out was filtered off, washed with water (25 ml) dried under high vacuum to yield nearly 90 % pure sulfone 52 (0.45 g, 84.90 %). This was used without purification for further reactions.(OXONE = $KHSO_5$, $KHSO_4$, K_2SO_4; 2:1:1).

Partial ^{1}H NMR : 7.18 (d, 2H, 8.58 hz), 6.8 (d, 2H, 8.58 hz), 5.6 (br, 1H), 3.92-4.08 (m, 2H, $SO_2CH_2CO_2CH_3$), 3.85 (s, 3H, -OCH_3).

IR(KBr): 3500-3400 br, 2920, 2890, 1680-1625 br, 1525, 1445, 1225, 1080 cm^{-1}

ESI MS(ES+): for $C_{51}H_{81}N_7O_{19}S$

Calculated : 1128.289

Found :$(M+Na)^+$ = 1150.6 (base peak)

1034.5, 1144.6, 1012.5, 968.5, 808.6, 771.4, 567.4.

UV(MeOH): λ_{max}: 208, 223, 276 nm (ε = 43326, 31366, 3587)

Compound 54 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-cyano-23-((1S,2S)-1,2-dihydroxy-2-(4-hydroxyphenyl)ethyl)-2,11,15-trihydroxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c:2,1-/]-[1,4,7,10,13,16]hexaaza-cyclohenicosin-9-yl]-12-methyltetradecanamide.

A solution of ornithine-5-sulfone 52 (0.5 g, 0.443 mmol) and sodium cyanide (0.1 g, 2.04 mmol) in anhydrous N,N-dimethylformamide (10 ml), under nitrogen

atmosphere was stirred at ambient temperature for 1 hr. Reaction progress was monitored by TLC (20 % MeOH/$CHCl_3$). The reaction mixture was diluted with water (150 ml), extracted with n-BuOH (3 x 100 ml), washed with water (150 ml) followed by brine (150 ml). Combined organic extract was dried over anhydrous Na_2SO_4, filtered and was concentrated in vacuum to give a crude product. This was then dissolved in a minimum amount of MeOH (5 ml), adsorbed on silica gel (1:1 w/w), and was subjected to silica gel flash column chromatography. 0-20 % MeOH/$CHCl_3$ was used as 5 % step gradient elution. Evaporation of the appropriate fractions gave ornithine-5-cyanocompound 54 (0.16 g, 35.55 %). Yield is calculated from nearly 90 % pure starting compound.

Partial ^1H NMR : 7.18 (d, 2H, 8.55 hz), 6.78 (d, 2H, 8.55 hz), 5.17 (br, 1H).

^{13}C NMR Spectrum :

177.08, 176.94, 174.72, 174.31, 174.17, 174.08, 173.56, 173.47, 172.98, 172.81, 172.20, 171.28, 170.73, 159.21, 133.70, 130.52, 130.24, 119.69, 118.80, 117.04, 77.41, 76.60, 72.12, 71.83, 70.65, 69.93, 69.64, 69.00, 68.83, 64.27, 63.89, 63.31, 63.08, 59.38, 59.18, 58.06, 57.04, 56.38, 54.70, 54.42, 54.21, 53.69, 53.43, 52.28, 46.13, 39.89, 39.37, 38.56, 37.63, 36.94, 36.45, 36.19, 31.19, 31.57, 31.37, 31.28, 31.14, 31.05, 28.97, 27.84, 27.55, 21.06, 20.45, 12.56, 12.19, 12.04.

IR(KBr): 3330-3400 br, 2910, 2320(CN peak), 1650, 1620, 1510, 1430, 1370, 1230, 1070 cm^{-1}

ESI MS(ES+): for $C_{49}H_{76}N_8O_{15}$

Calculated : 1017.178

Found :$(M+Na)^+$ = 1039.6 (base peak)

999.6, 995.5, 887.4, 567.4.

UV(MeOH):- λ_{max}: 205, 223, 276 nm (ε = 16989, 10046, 986)

Compound 55 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-aminomethyl-23-((1S,2S)-1,2-dihydroxy-2-(4-hydroxyphenyl)ethyl)-2,11,15-trihydroxy-6-((1R)-1-hydroxyethyl)-20-hydroxy- methyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c:2,1-*f*][1,4,7,10,13,16] hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

To a saturated solution of ammonia in anhydrous methanol (10 ml) was added 53 (0.1 g, 0.098 mmol) and a catalytic amount of Raney Nickel (0.03 g). The reaction

vessel (hydrogenation bottle, 250 ml) was evacuated by aspirator and thoroughly purged with hydrogen (three times). The resulting heterogeneous mixture was stirred under hydrogen atmosphere at 45 lb/in^2 pressure for 4 hr. TLC analysis (20 % methanol/$CHCl_3$) showed complete conversion to a more polar product. The catalyst was filtered off through celite and the filtrate was concentrated under vacuum to give a crude product, which was subjected to reverse-phase (5g, C-18) flash column chromatography eluting with 50-90 % acetonitrile/water as 10 % step gradient. Lyophilization of the appropriate fractions provided 55 (0.053 g, 52.79 %).

Partial ^{1}H NMR : 7.18 (d, 2H, 8.50 hz), 6.8 (d, 2H, 8.50 hz), 2.1 (m, 2H), iminol proton shifted upfield.

ESI MS(ES+): for $C_{49}H_{80}N_8O_{15}$

Calculated : 1021.210

Found :$(M+Na)^+$ = 1043.5 (base peak)

1019.4, 985.6, 852.8, 778.7, 760.7, 516.1, 392.4.

UV(MeOH): λ_{max}: 206, 225, 277 nm (ε = 29806, 26711, 6481)

Compound 56 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-23-((1S,2S)-1,2-dihydroxy-2-(4-hydro- xyphenyl)ethyl)-2,11,15-trihydroxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-12-(2-morpholinoethylamino)-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c:2,1-*f*] [1,4,7, 10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

To a stirred solution of ornithine-5-sulfone 52 (0.1 g, 0.089 mmol) in anhydrous 1,4-dioxane (10 ml), under nitrogen atmosphere was added 4-(2-aminoethyl) morpholine (0.495 g, 3.8 mmol) and the reaction mixture was stirred at 25-60°C for 1 hr. Reaction progress was monitored by TLC (20 % MeOH/$CHCl_3$). The reaction work-up was similar to that described for compound 54. Crude product was purified by using reverse-phase (4 g, C-18) flash column chromatography eluting with 50-90 % acetonitrile/water as 10 % step gradient. Lyophilization of the appropriate fractions provided 56 (0.07 g, 70.5 %) Yield is calculated from nearly 90 % pure starting compound.

Partial ^{1}H NMR : 7.2 (d, 2H, 8.55 hz), 6.8 (d, 2H, 8.55 hz), 5.04 (br, 1H), 3.7-3.8 (m, 4H), 2.35-2.2 (m, 8H).

IR(KBr): 3300-3400 br, 2930, 1680-1620 br, 1520, 1435, 1380, 1260, 1070 cm^{-1}

ESI MS(ES+): for $C_{54}H_{89}N_9O_{16}$

Calculated : 1120.341

Found :$(M+Na)^+$ = 1142.6 (base peak)

1130.6, 540.3.

Compound 57 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-(1H-1,3-diazolo-1-yl)-23-((1S,2S)-1,2-dihydroxy-2-(4-hydroxyphenyl)ethyl)-2,11,15-trihydroxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c:2,1-/][1,4,7,10, 13,16] hexaazacyclohenicosin-9-yl]-12-methyltetradecanamide.

To a stirred solution of ornithine-5-sulfone 53 (0.1 g, 0.089 mmol) in anhydrous 1,4-dioxane (10 ml), under nitrogen atmosphere was added imidazole (0.024 g, 0.356 mmol) and the reaction mixture was stirred at 25-60°C for 1 hr. Reaction progress was monitored by TLC (20 % MeOH/$CHCl_3$). After one hour the reaction mixture was diluted with water (100 ml), extracted with n-BuOH (3 x 50 ml), washed with water (100 ml) followed by brine (100 ml). Combined organic extract was dried over anhydrous Na_2SO_4 and was concentrated in vacuum to give a crude product. The crude product was purified by using reverse-phase (5g, C-18) flash column chromatography eluting with 50-90 % acetonitrile/water as 10 % step gradient. Lyophilization of the appropriate fractions provided 57 (0.06 g, 64.03 %) Yield is calculated from nearly 90 % pure starting compound.

Partial ^1H NMR : 7.8 (s, 1H), 7.65 (br s, 2H), 7.18, (d, 2H, 8.55 hz),6.8(d, 2H, 8.55 hz), 5.30 (br s, 1H).

IR(KBr): 3350-3400 br, 2931, 1650 br, 1620, 1520, 1455, 1390, 1225, 1065 cm^{-1}

ESI MS(ES+) : for $C_{51}H_{79}N_9O_{15}$

Calculated : 1058.230

Found : (M^+) = 1058.6

1044.6, 1012.4, 968.5, 848.5, 771.3, 567.4

Note Starting compound (ornithine-5 and homo-tyrosine-4-disulfone mulundocandin) for the preparation of compounds 57, 58 and 59, was prepared from thioether 49 using the process outlined for preparation of compound 52.

Compound 58 :
N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-cyano-23-((1S)-2-cyano-1-hydroxy-2-(4-hydroxyphenyl)ethyl)-2,11,15-trihydroxy-6-((1R)-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c:2,1-/][1,4,7,10,13,16]hexaaza- cyclo henicosin-9-yl]-12-methyltetradecanamide.
Using the process outlined for the preparation of 53, a solution of ornithine-5 & homo-tyrosine-4-disulfone mulundocandin (0.5 g, 0.4 mmol) and anhydrous sodium cyanide (0.2 g, 4.08 mmol) in anhydrous N,N-dimethylformamide (10 ml), under nitrogen atmosphere was stirred at ambient temperature for 1 hr to yield dicyanomulundocandin 58 (0.19 g, 46.22 %).
Partial ^{1}H NMR : 7.2 (d, 2H, 8.22 hz), 6.85 (d, 2H, 8.22 hz), iminol proton shifted upfield.
IR(KBr): 3330-3400 br, 2910, 2320(CN peak), 1650, 1620, 1510, 1430, 1370, 1230, 1070 cm^{-1}
ESI MS(ES+): for $C_{50}H_{75}N_9O_{14}$
Calculated : 1026.189
Found :$(M+Na)^+$ = 1048.5 (base peak)
1004.2, 887.3.

Compound 59 :
N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-12-azido-23-((1R)-2-azido-1-hydroxy-2-(4-hydroxyphenyl)ethyl)-2,11,15-trihydroxy-6-((1R)-1-hydroxyethyl)-20-hydroxymethyl-16-methyl-5,8,14,19,22,25-hexaoxoperhydrodiazolo[2,1-c:2,1-/][1,4,7,10,13,16]hexaaza- cyclohenicosin-9-yl]-12-methyltetradecanamide.
Using the process outlined for the preparation of 54, a solution of ornithine-5 & homo-tyrosine-4-disulfone mulundocandin (0.2 g, 0.16 mmol), anhydrous sodium azide (0.104 g, 1.6 mmol) in anhydrous 1,4-dioxane (10 ml), was stirred at 25-50°C for 2 hr. Crude product was purified by using semi preparative HPLC. (semiprep RP-18 column, 250 x 16 mm, 10μ particle size, 70 % acetonitrile/water as a eluant, 8 ml/min. flow rate, λ = 220 & 270 nm). Lyophilization of the appropriate fractions provided 59 (0.115 g, 67.84 %). Yield is calculated from nearly 90 % pure starting compound.

Partial ^{1}H NMR : 7.28, 7.14 (2 x d, 2H, 8.88 hz), 6.83 (t, 2H, 8.88 hz), 5.39(d, 1H, 1.86 hz).

IR(KBr): 3300-3400 br, 2930, 2100(sharp), 1650, 1620, 1515, 1440, 1240, 1070 cm^{-1}

ESI MS(ES+): for $C_{48}H_{75}N_{13}O_{14}$

Calculated : 1058.194

Found : $(M+Na)^+$ = 1080.5

1037.6, 873.9, 816.6, 567.0.

UV(MeOH): λ_{max}: 206, 221, 275 nm (ε = 21163, 8266, 1985)

Compound 60 :

N1-[(6S,9S,14aS,15S,16S,20S,23S,25aS,2R,11R)-2,11,15-trihydroxy-6-((1R)-1-hydroxy- ethyl)-23-((1R,2R/S)-1-hydroxy-2-(4-hydroxyphenyl)-2-(2-morpholinoethyl-amino)ethyl)-20-hydroxymethyl-16-methyl-12-(2-morpholinoethylamino)-5,8,14,19,22,25-hexaoxoper- hydrodiazolo[2,1-c:2,1-*f*][1,4,7,10,13,16]hexaazacyclohenicosin-9-yl]-12-methyltetradeca- namide.

Using the process outlined for the preparation of 54, a solution of ornithine-5 & homo-tyrosine-4-disulfonemulundocandin (0.2 g, 0.16 mmol), 4-(2-aminoethyl)morpholine (0.208 g, 1.6 mmol) in anhydrous 1,4-dioxane (10 ml), was stirred at 25-50°C for 2 hr. Crude product was purified by using semi preparative HPLC. (semiprep RP-18 column, 250 x 16 mm, 10μ particle size, 70 % acetonitrile/water as a eluant, 8 ml/min. flow rate, λ = 220 & 270 nm). Lyophilization of the appropriate fractions provided 60 (0.093 g, 43.89 %). Yield is calculated from nearly 90 % pure starting compound.

Partial ^{1}H NMR : 7.26 (t, 2H, 8.55 hz), 6.8 (d, 2H, 8.55 hz), 5.04 (br, 1H), 3.7-3.8 (m, 8H), 2.4-2.27 (m, 16H).

IR(KBr): 3300-3400 br, 2930, 1680-1620 br, 1520, 1435, 1380, 1260, 1070 cm^{-1}

ESI MS (ES+): for $C_{60}H_{101}N_{11}O_{16}$

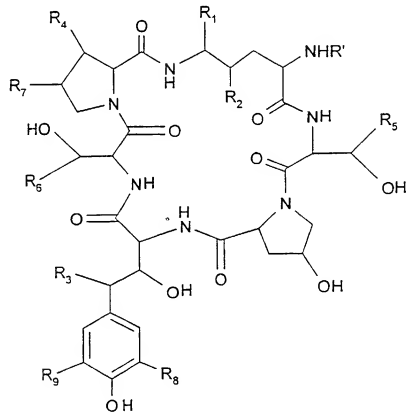
Calculated : 1232.516

Found : $(M+Na)^+$ = 1254.8 (base peak)

1133.6, 990.6, 946.4, 302.8.

Claims:

1. A cyclohexapeptide compound of the general formula I ;



I

wherein,

R^1 is C_1-C_{20} alkyl; C_9-C_{20} alkenyl; C_9-C_{20} alkoxyphenyl; an aryl group selected from: phenyl, biphenyl, terphenyl and naphthyl; C_1-C_{12} alkylpenyl, C_2-C_{12} alkenylphenyl, C_1-C_{12} alkoxyphenyl; linoleoyl; palmitoyl; 12-methylmyristoyl; 10,12-dimethylmyristoyl; or -$COC_6H_4(p)OC_8H_{17}$,

R_1 and R_3 are independently -OH; -CN; -CH_2NH_2; -N_3; aryl; substituted aryl; heterocyclyl and substituted heterocyclic with 1-3 of the same or different heteroatoms; aminoalkylamino; mono or di-substituted linear or cyclic aminoalkylamino; -OR, wherein, R is C_1-C_{12} alkyl; substituted alkyl of the type -$(CH_2)_n$-X, where n is 1-5 and X is Cl, Br, I, COOY, CN, NH_2 or a heterocyclic and where Y is C_1-C_6 linear or branched alkyl; C_2-C_{12}-alkenyl; aryl; fused aryl; substituted aryl; a heterocyclic containing 1-3 heteroatoms; mono or di-

substituted aminoalkyl; or a hydroxy protecting group; and R_3 may additionally be imidazolyl.

R_2 and R_4 are independently -H or –OH;

R_5 is -H or $-CH_3$.

R_6 is -H, $-CH_3$ or $-CH_2CONH_2$.

R_7 is -H, $-CH_3$ or -OH.

R_8 and R_9 are independently -H or $-CH_2$-Sec.amine in which the sec.amine is attached to $-CH_2$ through its N linkage;

and its pharmaceutically acceptable salts.

2. A compound of the formula I as claimed in claim 1 wherein R_1 is –OH or OR, and R_3 is –OH, -OR or imidazolyl wherein R in each case is C_1-C_{12} alkyl , substituted alkyl of the type $-(CH_2)_n$-X, where n is 1-5, X is Cl, Br, I, COOY, CN, NH_2 or a heterocyclic and Y is a C_1-C_6 linear or branched alkyl; $-C_2$-C_{12}-alkenyl; ary; fused aryl; substituted aryl; a heteroaryl containing 1-3 heteroatoms; a heterocyclic containing 1-3 heteroatoms; mono or di-substituted aminoalkyl; or a hydroxy protecting group.

3. A compound of the formula I as claimed in claim 1 or claim 2 wherein R^1 is linoleoyl, palmitoyl, 12-methylmyristoyl, 10, 12-dimethylmyristoyl or – $COC_6H_{4(p)}OC_8H_{17}$.

4. A compound of the formula I as claimed in claim 1, 2 or 3, wherein to the nitrogen atom of the secondary amine are attached the same or different groups selected from: C_1-C_{12} alkyl, C_2-C_{12} alkenyl, aryl, substituted aryl, alkylaryl and substituted alkylaryl, or the nitrogen atom of the secondary amine is part of a heterocyclic group, optionally substituted by one or more of: C_1-C_6 alkyl, C_1-C_6 alkenyl, aryl, amino, nitro and halogen, or a fused heterocyclic group, whereby the heterocyclic group contains 1-3 of the same or different heteroatoms.

5. A compound of the formula I as claimed in any one of the preceding claims, wherein the secondary amine is selected from: piperidine, pyrrolidine, 4-methylpiperidine, morpholine, dimethylamine, diisopropylamie, 4-piperidino-piperidine, piperazine, 1-methylpiperazine, 1-(2-fluorophenyl)piperazine, 1-(2-chlorophenyl)piperazine, 1-(2-pyrimidyl)piperazine, 1-(4-fluorophenyl)piperazine, N-(α,α,α-trifluoro-m-tolyl)piperazine, 1-phenylpiperazine, 1-benzylpiperazine, 1-(2-pyridyl)piperazine, 1-(4-pyridyl)piperazine, 1-(4-methylphenyl) piperazine, 1-(2,6-dimethylphenyl)piperazine, 1-(1-phenylethyl)piperazine, dibenzylamine, N-(tert-butyl)benzylamine and N-(isopropyl)benzylamine.

6. A compound of the formula I as claimed in claim 1, wherein R^1 is 12-methylmyristoyl, R_1 and R_3 are independently -OH, -CN, $-CH_2NH_2$, $-N_3$, aryl, substituted aryl, heterocyclyl and substituted heterocyclyl having 1-3 of the same or different heteroatoms, aminoalkylamino, or mono or di-substituted linear or cyclic aminoalkylamino, R_5 and R_7 are both $-CH_3$, R_6 is –H, and R_8 and R_9 are both –H.

7. A pharmaceutical composition comprising an effective amount of the compound of the formula I or a pharmaceutically acceptable salt thereof as claimed in any one of the preceding claims, and a pharmaceutically acceptable carrier.

8. A compound of the formula I as claimed in any one of claims 1 to 6 or a pharmaceutically acceptable salt thereof for use as an anti-fungal agent.

9. A process for the production of a compound of the general formula I as claimed in claims 1-5 , comprising the steps of:

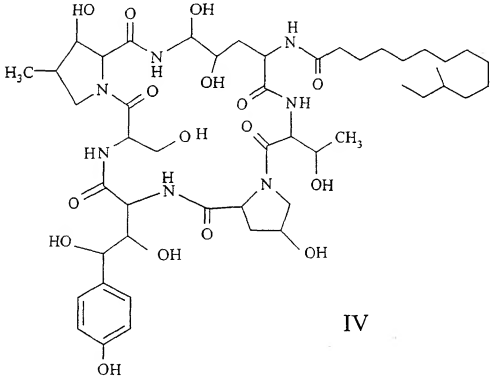
a) reacting a cyclohexapeptide compound of the formula I, wherein R^1, R_2, R_4, R_5, R_6 and R_7 are as defined in claim 1, 2 or 3 , R_1 and R_3 are both –OH, and R_8 and R_9 are -H , with an alcohol in the presence of an acid in an aprotic solvent at a temperature ranging from 0°C to 60° to obtain the corresponding cyclohexapeptide derivative of the formula I wherein R^1, R_2,

R_4, R_5, R_6 and R_7 are as defined in claim 1, 2 or 3, R_1 and R_3 are independently –OH or –OR such that at least one of R_1 or R_3 is -OR, wherein R is C_1-C_{12} alkyl, C_2-C_{12} alkenyl, fused aryl, substituted aryl, a heterocyclyl containing 1-3 heteroatoms, mono or di-substituted aminoalkyl, or a hydroxy protecting group, and R_8 and R_9 are -H;

b) reacting the compounds obtained in step (a) with a secondary amine in presence of paraformaldehyde in an aprotic solvent at a temperature ranging from 60°C to 150°C to yield the desired compound of formula I, isolating and purifying the resulting compound of formula I from the reaction mixture in a known manner and if desired, converting the compound of formula I into its pharmaceutically acceptable salt in a known manner.

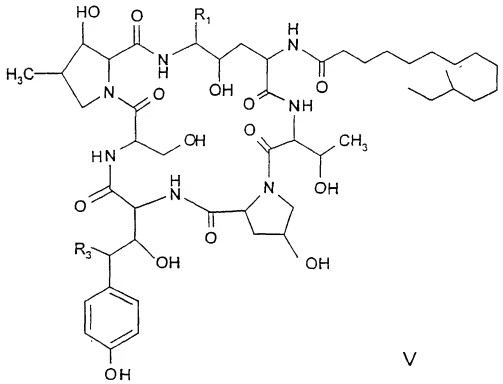
10. A process for the preparation of a cyclohexapeptide compound of the formula I as claimed in any one of claims 1 to 6, comprising the steps of :

a) reacting mulundocandin of the following formula IV,



IV

with a nucleophile in presence of an acid in an aprotic solvent at a temperature ranging from 0°C to 60° to obtain the corresponding cyclohexapeptide derivative of formula V;



V

wherein R_1 and R_3 are –OH or –SR such that at least one of R_1 or R_3 is -SR wherein R in each case is C_1-C_{12} alkyl, substituted alkyl of the type -$(CH_2)_n$-X, wherein n is 1-5 and X is Cl, Br, I, COOY, CN, NH_2, or a heterocyclic, Y is C_1-C_6 linear or branched alkyl chain; C_2-C_{12} alkenyl; aryl; fused aryl; substituted aryl;

a heterocyclyl containing 1-3 heteroatoms; mono or di-substituted aminoalkyl; or a hydroxy protecting group ;

b) reacting the compounds of formula V as obtained in step (a) with an oxidising agent in an aqueous medium at a temperature ranging from 20°C to 60°C to obtain the corresponding sulfones (VI), wherein R_1 and R_3 are –OH or -S

$(O_2)R$, such that at least one of R_1 or R_3 is $-SO_2R$, wherein R is a C_1-C_{12} alkyl, substituted alkyl of the type $-(CH_2)_n-X$, wherein n is 1-5 and X is Cl, Br, I, COOY, CN, NH_2, a heterocyclic, Y is a C_1-C_6 linear or branched alkyl chain; C_1-C_{12} alkenyl; aryl; fused aryl; substituted aryl; a heterocyclyl containing 1-3 heteroatoms; mono or di-substituted aminoalkyl; or a hydroxy protecting group;

c) reacting the sulfone (VI) obtained in step (b) with a nucleophile in a solvent at a temperature ranging from 20°C to 60°C to obtain the desired compound of the formula I, isolating and purifying the resulting compound of the formula I from the reaction mixture in a known manner and if desired, converting the compound of formula I into its pharmaceutically acceptable salt in a known manner.

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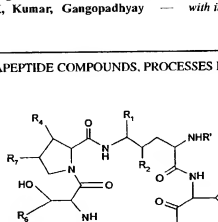
[Continued on next page]

(54) **Title:** NOVEL CYCLOHEXAPEPTIDE COMPOUNDS, PROCESSES FOR THEIR PRODUCTION AND THEIR USE AS A PHARMACEUTICAL



(I)

(57) Abstract: A cyclohexapeptide compound of general formula (I), wherein R^1 is C_1-C_{20} alkyl; C_9-C_{20} alkenyl; C_9-C_{20} alkoxyphenyl; an aryl group selected from: phenyl, biphenyl, terphenyl and naphthyl; C_1-C_{12} alkylphenyl, C_2-C_{12} alkenylphenyl, C_1-C_{12} alkoxyphenyl; linoleoyl; palmitoyl; 12-methylmyristoyl; 10,12-dimethylmyristoyl; or $-COC_6H_4(p)OC_9H_{17}$, R_1 and R_3 are independently -OH; -CN; $-CH_2NH_2$; $-N_3$; aryl; substituted aryl; heterocyclyl and substituted heterocyclic with 1-3 of the same or different heteroatoms; aminoalkylamino; mono or di-substituted linear or cyclic aminoalkylamino; -OR, wherein, R is C_1-C_{12} alkyl; substituted alkyl of the type $-(CH_2)_n$-X, where n is 1-5 and X is Cl, Br, I, COOY, CN, NH_2 or a heterocyclic and where Y is C_1-C_6 linear or branched alkyl; C_2-C_{12}-alkenyl; aryl; fused aryl; substituted aryl; a heterocyclic containing 1-3 heteroatoms; mono or di-substituted aminoalkyl; or a hydroxy protecting group; and R_3 may additionally be imidazolyl; R_2 and R_4 are independently -H or -OH; R_4 is -H or $-CH_3$. R_6 is -H, $-CH_3$ or $-CH_2CONH_2$. R_7 is -H, $-CH_3$ or -OH. R_8 and R_9 are independently -H or $-CH_2$-Sec.amine in which the sec.amine is attached to $-CH_2$ through its N linkage; and its pharmaceutically acceptable salts. The compounds are useful as antifungal agents.

WO 01/07468 A3

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DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION

☒ Declaration Submitted with Initial Filing OR ☐ Declaration Submitted after Initial Filing

Attorney Docket Number	146.1380
First Named Inventor	L. BANSI et a;
COMPLETE IF KNOWN	
Application Number	PCT/EP00/06769
Filing Date	July 15, 2000
Group Art Unit	
Examiner Name	

As a below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

NOVEL CYCLOHEXAPEPTIDE COMPOUNDS, PROCESSES FOR THEIR PRODUCTION AND THEIR USE AS A PHARMACEUTICAL

(Title of the Invention)

the specification of which

☐ is attached hereto

OR

☒ was filed on (MM/DD/YYYY) July 15, 2000 as United States Application Number or PCT International Application Number PCT/EP00/06769 and was amended on (MM/DD/YYYY) _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37 Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code §119 (a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate, or §365 (a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached? YES	Certified Copy Attached? NO
99114649.9	Europe	7/27/99	☐	☐	☐
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐

☐ Additional foreign application numbers are listed on a supplemental priority sheet attached hereto:

I hereby claim the benefit under Title 35, United States Code §119(e) of any United States provisional application(s) listed below.

Application Number(s)	Filing Date (MM/DD/YYYY)

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DECLARATION

I hereby claim the benefit under Title 35, United States Code §120 of any United States application(s), or §365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code §112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

U.S. Parent Application Number	PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	Parent Patent Number (if applicable)

☐ Additional U.S. or PCT international application numbers are listed on a supplemental priority sheet attached hereto.

As a named inventor, I hereby appoint the following registered practitioner(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

Name	Registration Number	Name	Registration Number
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Jordan B. Bierman	18,629		
Donald C. Lucas	~~31,275~~		
Bierman, Muserlian and Lucas	18,818		

☐ Additional registered practitioner(s) named on a supplemental sheet attached hereto.

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City: New York | State: New York | ZIP: 10016

Country: U.S.A. | Telephone: (212) 661-8000 | Fax: (212) 661-8002

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name of Sole or First Inventor: ☐ A petition has been filed for this unsigned inventor

(10) Given Name: BANSI | Middle Initial: | Family Name: LAL | Suffix e.g. Jr.:

Inventor's Signature: Bansi Lal | Date: 16 Sept. 2002

Residence: City: Mumbai | State: | Country: India INR | Citizenship: IN

Post Office Address:

Post Office Address: 30 Advani Apartments Mulund (West)

City: Mumbai | State: | Zip: 400 080 | Country: India

☒ Additional inventors are being named on supplemental sheet(s) attached hereto

If added type a plus sign (+) inside this box → [+]

PTO/SB/01 (8-96)
Approved for use through 9/30/98. OMB 0651-0032
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
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DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION

Attorney Docket Number	146.1380
First Named Inventor	L. BANSI et al
COMPLETE IF KNOWN	
Application Number	PCT/EP00/06769
Filing Date	July 15, 2000
Group Art Unit	
Examiner Name	

☒ Declaration Submitted with Initial Filing OR ☐ Declaration Submitted after Initial Filing

As a below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

NOVEL CYCLOHEXAPEPTIDE COMPOUNDS, PROCESSES FOR THEIR PRODUCTION AND THEIR USE AS A PHARMACEUTICAL

(Title of the Invention)

the specification of which

☐ is attached hereto
OR
☒ was filed on (MM/DD/YYYY) July 15, 2000 as United States Application Number or PCT International

Application Number PCT/EP00/06769 and was amended on (MM/DD/YYYY) _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37 Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code §119 (a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate, or §365 (a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached? YES	NO
99114649.9	Europe	7/27/99	☐	☐	☐
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐

☐ Additional foreign application numbers are listed on a supplemental priority sheet attached hereto:

I hereby claim the benefit under Title 35, United States Code § 119(e) of any United States provisional application(s) listed below.

Application Number(s)	Filing Date (MM/DD/YYYY)

☐ Additional provisional application numbers are listed on a supplemental priority sheet attached hereto.

(January 1997)

Please type a plus sign (+) inside this box → + 146.1380

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DECLARATION

I hereby claim the benefit under Title 35, United States Code §120 of any United States application(s), or §365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code §112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

U.S. Parent Application Number	PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	Parent Patent Number (if applicable)

☐ Additional U.S. or PCT international application numbers are listed on a supplemental priority sheet attached hereto.

As a named inventor, I hereby appoint the following registered practitioner(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

Name	Registration Number	Name	Registration Number
Charles A. Muserlian	19,683		
Jordan B. Bierman	18,629		
Donald C. Lucas	31,275		
Bierman, Muserlian and Lucas	18,818		

☐ Additional registered practitioner(s) named on a supplemental sheet attached hereto.

Direct all correspondence to:

Name	Bierman, Muserlian and Lucas				
Address					
Address	600 Third Avenue				
City	New York	State	New York	ZIP	10016
Country	U.S.A.	Telephone	(212) 661-8000	Fax	(212) 661-8002

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name of Sole or First Inventor: ☐ A petition has been filed for this unsigned inventor

Given Name	BANSI	Middle Initial		Family Name	LAL	Suffix e.g. Jr.	
Inventor's Signature						Date	
Residence: City	Mumbai	State		Country	India	Citizenship	IN
Post Office Address							
Post Office Address	30 Advani Apartments Mulund (West)						
City	Mumbai	State		ZIP	400 080	Country	India

☒ Additional inventors are being named on supplemental sheet(s) attached hereto

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146.1380

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DECLARATION

ADDITIONAL INVENTOR(S) Supplemental Sheet

Name of Additional Joint Inventor, if any: ☐ A petition has been filed for this unsigned inventor

Given Name	Middle Initial	Family Name	Suffix (e.g. Jr)
VITTHAL	G	GUND	

Inventor's Signature: [signature] Date: 25/09/2002

Residence: City: Sherbrooke, Québec State: Country: CANADA CAN Citizenship: IN

Post Office Address:

Post Office Address: 2145 Rue Galt Ouest, Appt. 427

City: Sherbrooke, Québec State: Zip: J1K 3A7 Country: CANADA

Name of Additional Joint Inventor, if any: ☐ A petition has been filed for this unsigned inventor

Given Name	Middle Initial	Family Name	Suffix (e.g. Jr)
ASHOK	K.	GANGOPADHYAY	

Inventor's Signature: Date:

Residence: City: Mumbai State: Country: India Citizenship: IN

Post Office Address:

Post Office Address: K-33 Hoechst Quarters, Darga Road, Amarnagar, Mulund (West)

City: Mumbai State: Zip: 400 080 Country: India

Name of Additional Joint Inventor, if any: ☐ A petition has been filed for this unsigned inventor

Given Name	Middle Initial	Family Name	Suffix (e.g. Jr)

Inventor's Signature: Date:

Residence: City: State: Country: Citizenship:

Post Office Address:

Post Office Address:

City: State: Zip: Country:

Name of Additional Joint Inventor, if any: ☐ A petition has been filed for this unsigned inventor

Given Name	Middle Initial	Family Name	Suffix (e.g. Jr)

Inventor's Signature: Date:

Residence: City: State: Country: Citizenship:

Post Office Address:

Post Office Address:

City: State: Zip: Country:

☐ Additional inventors are being named on supplemental sheet(s) attached hereto

(January 1997)

[redacted]

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Given Name	Middle Initial	Family Name	Suffix e.g. Jr.
VITTHAL	G.	GUND	

Inventor's Signature | Date

Residence: City	State	Country	Citizenship
Mumbai		India	IN

Post Office Address

Post Office Address: K-1 Hoechst Quarters, Darga Road, Amarnagar, Mulund (West)

City	State	Zip	Country
Mumbai		400 080	India

30 Name of Additional Joint Inventor, if any: ☐ A petition has been filed for this unsigned inventor

Given Name	Middle Initial	Family Name	Suffix e.g. Jr.
ASHOK	K.	GANGOPADHYAY	

Inventor's Signature: Agangopadhyay. Date: 16.9.02

Residence: City	State	Country	Citizenship
Mumbai		India INK	IN

ost Office Address

Post Office Address: K-33 Hoechst Quarters, Darga Road, Amarnagar, Mulund (West)

City	State	Zip	Country
Mumbai		400 080	India

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Given Name	Middle Initial	Family Name	Suffix e.g. Jr.

Inventor's Signature | Date

Residence: City	State	Country	Citizenship

Post Office Address

Post Office Address

State	Zip	Country

Name of Additional Joint Inventor, if any: ☐ A petition has been filed for this unsigned inventor

Given Name	Middle Initial	Family Name	Suffix e.g. Jr.

In[illegible]tor's S[illegible]ure | Date

Residence: City	State	Country	Citizenship

Post Office Address

Post Office Address

City	State	Zip	Country

☐ Additional inventors are being named on supplemental sheet(s) attached hereto

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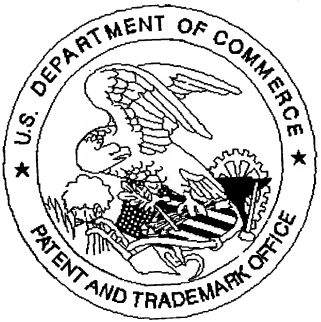

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